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V. V. Benberin[1], G. A. Yermakhanova[2], A. A. Akhetov[2], T. A. Vochshenkova[2], N. A. Shanazarov[2], A. Y. Naurazbayeva[2]

[1]Medical Center of President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan,
[2]Medical Center Hospital of President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.
E-mails: valeriy-benberin@mail.ru, ermakhanova@gmail.com, amir.akhetov.a@gmail.com, vochshenkova@gmail.com, nasrulla@inbox.ru, anar.naurazbayeva@gmail.com

EFFECTIVENESS AND SAFETY OF VACCINATION FOR PREVENTING PNEUMOCOCCAL INFECTION IN ADULT PATIENTS: REVIEW OF INTERNATIONAL RECOMMENDATIONS AND STUDIES

Abstract. *Purpose of review:* to summarize the effectiveness and safety of vaccination for preventing pneumococcal infection, namely community-acquired pneumonia among adult patients.

Materials and methods: a literature search for international recommendations and studies was conducted in electronic databases and publications included in Embase, PubMed/Medline, Science Direct, eLibrary. More than 20 publications were selected and reviewed, including full-text articles, Systematic Reviews and Meta-Analysis that were published in English. The depth of the literature search was 8 years.

Results and conclusions: currently, international organizations recommended the routine use of the 13-valent conjugate vaccine (PCV13) sequentially with the 23-valent polysaccharide vaccine (PPSV23) for all adults aged 65 years and over. However, some studies indicate that repeated vaccination has no effect, since pneumococcal polysaccharide capsular antigens elicit an immune response by a T-cell independent mechanism.

Keywords: vaccination, community-acquired pneumonia, 13-valent pneumococcal conjugate vaccine, 23-valent pneumococcal polysaccharide vaccine.

Introduction. Pneumococcus (Streptococcus pneumoniae) remains the main causative agent of pneumococcal infections and can cause a wide range of diseases [1]. Pneumococcal infection causes pneumonia, meningitis, middle ear infections (otitis media), sinusitis, and sepsis. Currently, according to the data of foreign authors, pneumococcus is responsible for 25-35% of all community-acquired pneumonia and 3-5% of hospital- acquired pneumonia.

Community-acquired pneumonia is an acute disease that has arisen in out-of-hospital conditions, accompanied by symptoms of infection of the lower respiratory tract and radiographic signs in the lungs in the absence of an obvious diagnostic alternative. Among adult patients, community-acquired pneumonia is a common type of pneumococcal infection [2] and it is difficult on the background of comorbid conditions (cardiovascular diseases, oncological and hematological diseases, diabetes, renal and liver diseases, and others). In elderly patients, the risk of death from community-acquired pneumonia and its complications is 3-5 times higher than that of young patients, estimated at 5-7%.

Treatment of pneumococcal infections with penicillin and other drugs was quite effective until some strains of the disease became resistant to these drugs. Therefore, to date, vaccination is the most effective method of preventing pneumococcal infections. According to the World Health Organization (WHO), in the world, life expectancy has increased by 20-30 years due to mass immunization. Every year, more than 2 million lives are saved thanks to immunization. According to WHO's position, vacci-nation of all age groups of the population is the only way to significantly affect morbidity and mortality from pneumo-

coccal infection and it is considered necessary to include routine vaccinations against pneumococcal infection in national calendars of all countries.

The purpose of this review is summarize the effectiveness and safety of vaccination for preventing pneumococcal infection, namely community-acquired pneumonia among adult patients.

Pneumococcal vaccines. To prevent diseases caused by pneumococcus, two vaccines are recommended worldwide that are available for adult vaccination: a 13-valent conjugate vaccine (PCV13) and a 23-valent polysaccharide vaccine (PPSV23).

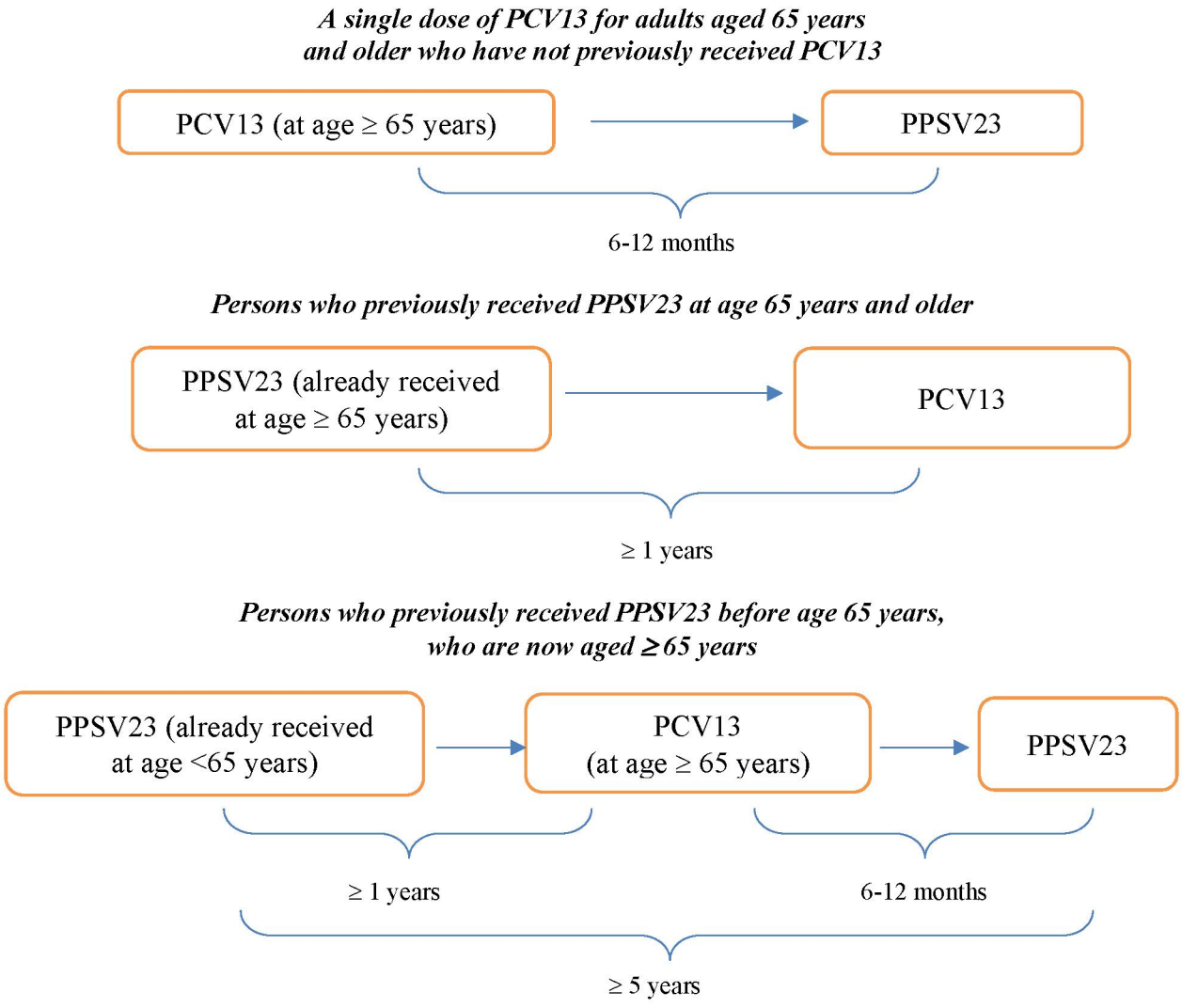
PCV13 is inactivated and consists of capsular polysaccharides of thirteen serotypes of pneumococcus, individually conjugated to a carrier protein. In the European Union, PCV13 is approved for use from 6 weeks without further age restriction.

PPSV23 consists of capsular polysaccharides of 23 serotypes of pneumococcus (12 serotypes together with PCV13 and 11 additional serotypes). Basically, people need one dose of PPSV23, and the second dose is recommended for certain risk groups.

In 2010, the American Advisory Committee on Immunization Practices (ACIP) approved revised recommendations that all persons should be vaccinated with PPSV23 at the age of 65 years.

In 2012, ACIP developed recommendations for the use of PCV13 and PPSV23 for adults aged 19 years and older with immunocompromising conditions.

According to the recommendations of ACIP, adult vaccination should be started with PCV13 (scheme).



Sequential administration and recommended intervals for PCV13 and PPSV23 (ACIP recommendations)

A single dose of PCV13 is recommended for adults aged 65 and older who have not previously received PCV13. Even if the patient has previously been vaccinated with PPSV23, one dose of PCV13 is needed. The dose of PPSV23 should be given 6–12 months after a dose of PCV13. The two vaccines should not be coadministered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks. Adults aged 65 years and older who have previously received one dose of PPSV23 also should receive a dose of PCV13 if they have not yet received it. The dose of PCV13 should be given ≥1 year after the most recent dose of PPSV23 is received. For those with an additional dose of PPSV23, this subsequent dose of PPSV23 should be given 6–12 months after PCV13 and ≥5 years after the most recent dose of PPSV23 [3]. According to these recommendations for the routine use of PCV13 among adults aged 65 and over will be revised in 2018 [4].

Materials and methods. A literature search for international recommendations and studies was conducted in electronic databases. More than 20 publications were selected and reviewed, including full-text articles, Systematic Reviews and Meta-Analysis included in Embase, PubMed/Medline, Science Direct, eLibrary, and open access publications from the WHO resource, the Centers for Disease Control and Prevention (CDC).

The depth of the literature search was 8 years (2008-2016). The following search terms were used: “23-valent polysaccharide vaccine”, “13-valent conjugate vaccine”, “efficacy/effectiveness of PPV23”, “efficacy/effectiveness of PCV13”, “pneumococcal disease”, “community-acquired pneumonia”, “pneumococcal vaccination”, “randomly”, and “randomised”.

Results. *Evidence supporting PCV13 vaccination among adults.* At the end of 2011, PCV13 was approved by the Food and Drug Administration (FDA) and in early 2012, respectively, by the European Medical Association of the countries of the European Union for use among adults aged 50 and over [5, 6]. The FDA identified a "significant therapeutic benefit compared to existing treatment methods" as protection for adults aged 50 years and older from pneumococcal pneumonia [7].

The effectiveness of PCV13 has been proven by a large-scale scientific study "Community-Acquired Pneumonia Immunization Trial in Adults" (CAPiTA), aimed at evaluating the effectiveness of PCV13 in preventing pneumococcal pneumonia caused by one of the pneumococcal serotypes contained in the vaccine.

The CAPiTA was the largest double-blind, randomized placebo-controlled trial in the Netherlands involving approximately 85,000 patients aged 65 years and older. The CAPiTA trial confirmed the efficacy of the PCV13 vaccine and demonstrated a reduction in the number of causes of pneumonia in adult patients aged 65 years and older who received PCV13 compared with placebo [8, 9]. The evidence supporting the efficacy of PCV13 vaccination in adults was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [10] framework and was published in 2014 [11].

The CAPiTA trial did not reveal any safety problems associated with the use of PCV13 in more than 42,000 patients who had been vaccinated. The effectiveness of PCV13 for the prevention of community-acquired pneumonia and invasive pneumococcal infection persists for at least 4 years. These data are consistent with observations of previous trials of PCV13 vaccination among adults [12].

Using the results of a CAPiTA trial and a number of other epidemiological studies that were conducted in parallel to the Netherlands, the cost-effectiveness of PCV13 vaccination [13] was evaluated among people of different ages and risk groups. The approach of using PCV13 in different strategies (different ages, risk groups, etc.) was considered. The results of the study showed that PCV13 in the Netherlands proved to be cost-effective.

In addition, a study [14] on the effect of age on the efficacy of PCV13 in the elderly was conducted. In this study, the efficacy of PCV13 in the prevention of community-acquired pneumonia or invasive pneumococcal infection was highest among adults aged 65 years and older and the efficacy of the vaccine decreased with increasing age.

However, in the CAPiTA trial, immunogenicity data collected at 1, 12 and 24 months after vaccination indicated only small differences in the levels of antibodies to immunoglobulin G and opsonophagocytic activity titers in adults, compared to younger subjects [15]. Two of the most common PCV13 serotypes (3 and 7F) were less common in the highest age group and had a higher overall vaccine efficacy. Nevertheless, the effectiveness of the vaccine also decreased with age for these serotypes.

Evidence supporting PPSV23 vaccination among adults. At the end of 2010, ACIP updated recommendations for the prevention of invasive pneumococcal infections with PPSV23 vaccine in adults aged 65 years and older and patients aged 19-64 with risk factors for severe pneumococcal infections. There are a number of studies that prove the effectiveness of PPSV23 in adults.

In the United Kingdom, the National Health Service recommends only the use of the PPSV23 vaccine among people aged 65 years and older who are in good health, and among people suffering from a disease exposing them to the risk of pneumococcal infection; and revaccination is intended for these people every 5 years.

In the United States, pneumococcal vaccination is recommended using the PCV13 and PPSV23 vaccine sequence among people older than 2 years with risk factors for pneumococcal infection.

In Germany, PPSV23 vaccination of all 60 year olds and elderly people has been recommended since 1998. According to the "Health Study on Adults in Germany", coverage of the current vaccine is 30% between the ages of 65 and 79 years old. Standing Committee on Vaccination (STIKO) recommends the use of PPSV23 only at the age of 60 years and offers revaccination at intervals of >6 years [16].

The results of the analysis conducted, which is stratified by age, show that PPSV23 is effective in adults over the age of 40 compared with younger than 20 years [17]. Therefore, PPSV23 is more effective against community-acquired pneumonia in the elderly than in young people.

Many meta-analyzes have demonstrated that PPSV23 does not have a preventive effect on mortality from all causes [18, 19]. However, moderate evidence of the analysis conducted [17] in accordance with the GRADE framework showed that PPSV23 demonstrates a protective tendency to reduce mortality from pneumonia, but this result was not statistically significant. Although the observed protective effect of PPSV23 against pneumococcal pneumonia is statistically insignificant, the overall relative risk was 0.54, indicating a protective trend.

The results of the analysis, which included only three tests, were confirmed by very low quality indicators due to serious heterogeneity, indirectness and inaccuracy. Thus, the impact of PPSV23 on pneumococcal pneumonia requires further study.

In addition, there are no epidemiological data demonstrating the effectiveness of revaccination with PPSV23, although it would be difficult not to offer it especially for people who were vaccinated young. Revaccination for less than 5 years is not acceptable for reasons of tolerability, although 5 years after PPSV23, revaccination with PPSV23 may be suggested.

Conclusions. Based on the latest recommendations, currently, the Centers for Disease Control and Prevention, WHO, the Advisory Committee on Immunization Practices, the European Medicines Agency have recommended the routine use of the PCV13 vaccine sequentially with the PPSV23 vaccine for all adults aged 65 years and over [20, 3]. However, the issue of the need for revaccination against pneumococcal infection remains a subject of discussion. The results of some studies indicate that repeated vaccination has no effect, since pneumococcal polysaccharide capsular antigens elicit an immune response by a T-cell independent mechanism.

From the presented data it can be concluded that the vaccination of PCV13 and PPSV23 against the pneumococcal infections is clinically and cost-effective.

It is assumed that the review of international recommendations will optimize the management of adult patients with community-acquired pneumonia and develop a scientifically valid scheme for the use of pneumococcal vaccines in adult patients.

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В. В. Бенберин[1], Г. А. Ермаханова[2], А. А. Ахетов[2], Т. А. Вощенкова[2], Н. А. Шаназаров[2], А. Е. Науразбаева[2]

[1]Қазақстан Республикасы Президенті Іс Басқармасы Медициналық орталығы, Астана, Казақстан,
[2]Қазақстан Республикасы Президенті Іс Басқармасы Медициналық орталығы Ауруханасы, Астана, Казақстан

ЕРЕСЕК ПАЦИЕНТТЕРДЕ ПНЕВМОКОКК ИНФЕКЦИЯСЫНЫҢ ЕКПЕЛІК АЛДЫН АЛУ ТИІМДІЛІГІ ЖӘНЕ ҚАУІПСІЗДІГІ: ХАЛЫҚАРАЛЫҚ ҰСЫНЫСТАРДЫ ЖӘНЕ ЗЕРТТЕУЛЕРДІ ШОЛУ

Аннотация. *Мақсаты:* пневмококк инфекциясының екпелік алдын алу тиімділігі мен қауіпсіздігін зерттеу, атап айтқанда, ересек пациенттер арасындағы ауруханадан тыс пневмония.

Материалдар мен әдістер: Embase, Medline/PubMed, ScienceDirect, eLibrary кіретін жарияланымдарда және электрондық дерекқорларында халықаралық ұсыныстарға және жүргізілген зерттеулерге арналған

әдебиеттерді іздеу жүргізілді. 20-дан астам жарияланымдар таңдалып қарастырылды, соның ішінде ағылшын тіліндегі толық мәтінді мақалалар, жүйелі шолулар мен мета-анализдер таңдап алынды. Әдебиеттерді іздеу тереңдігі 8 жыл болды.

Нәтижелер мен қорытындылар: қазіргі уақытта халықаралық ұйымдар 65 жас және одан жоғары жастағы барлық ересектер үшін PCV13 вакцинасын PPSV23 вакцинасымен дәйекті түрде жүйелі пайдалануды ұсынды. Алайда, кейбір зерттеулер вакцинаны қайталап қолданудың ешқандай әсері жоқ екенін көрсетеді, өйткені пневмококк полисахаридті капсулярлық антигендер Т-тәуелсіз механизм арқылы иммундық жауапты тудырады.

Түйін сөздер: екпелік алдын алу, ауруханадан тыс пневмония, 13-валенттік конъюгирленген вакцина, 23-валенттік полисахаридті вакцина.

В. В. Бенберин[1], Г. А. Ермаханова[2], А. А. Ахетов[2], Т. А. Вощенкова[2], Н. А. Шаназаров[2], А. Е. Науразбаева[2]

[1]Медицинский центр Управления делами Президента Республики Казахстан, Астана, Казахстан,
[2]Больница Медицинского центра Управления делами Президента Республики Казахстан, Астана, Казахстан

ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ВАКЦИНОПРОФИЛАКТИКИ ПНЕВМОКОККОВОЙ ИНФЕКЦИИ У ВЗРОСЛЫХ ПАЦИЕНТОВ: ОБЗОР МЕЖДУНАРОДНЫХ РЕКОМЕНДАЦИЙ И ИССЛЕДОВАНИЙ

Аннотация. *Цель обзора:* изучение эффективности и безопасности вакцинопрофилактики пневмококковой инфекции, а именно внебольничной пневмонии среди взрослых пациентов.

Материалы и методы: проведен поиск литературы по международным рекомендациям и проведенным исследованиям в электронных базах данных и публикациях, вошедших в Embase, Medline/PubMed, Science Direct, eLibrary. Были выбраны и рассмотрены более 20 публикации, в том числе полнотекстовые статьи, систематические обзоры и мета-анализы на английском языке. Глубина поиска публикации составляла 8 лет.

Результаты и выводы: в настоящее время международными организациями рекомендовано рутинное использование вакцины PCV13 последовательно с вакциной PPSV23 всем взрослым в возрасте 65 лет и старше. Однако, некоторые исследования показывают, что повторное введение вакцины не оказывает эффекта, так как пневмококковые полисахаридные капсульные антигены вызывает иммунный ответ по Т-независимому механизму.

Ключевые слова: вакцинопрофилактика, внебольничная пневмония, 13-валентная конъюгированная вакцина, 23-валентная полисахаридная вакцина.

Authors:

Benberin V.V. – Doctor of medical sciences, professor, corresponding member of the National Academy of Sciences of Kazakhstan, head of the Medical Center of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.

Yermakhanova G.A. – Master of public health, head of Clinical trials Sector of the Center for Gerontology, Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.

Akhetov A.A. – Doctor of medical sciences, director of the Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.

Voshchenkova T.A. – Master of Business Administration, deputy head of the Gerontology Center, Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.

Shanazarov N.A. – Doctor of medical sciences, deputy director for science of the Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.

Naurazbayeva A.Y. – Master of ecology, specialist of Clinical Trials Sector of the Center for Gerontology, Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan.