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Repeated Annual Seasonal Influenza Vaccination of Patients With Circulatory Diseasы as Secondary Prevention of Cardiovascular Events: an Additional Self-Controlled Case Series Analysis

Aim To assess the effect of annual seasonal flu vaccination for 3 years on the risk of acute respiratory infection (ARI) and cardiovascular events (CVE) in cardiological patients followed up using two analytical methods.

Material and methods This prospective comparative study included 817 patients in October 2012. CVE, other chronic noncommunicable diseases, and ARI recorded from October 2012 through November 2015 were analyzed. Vaccinated and unvaccinated patients were compared using survival curves and a self-controlled case series method for paired 6-month periods. Differences were considered statistically significant at p<0.05.

Results The analysis included 813 patients (mean age, 63.3±11.6 years; 40.5% men; in the 2012/13-2013/14-2014/15 season, 45-44-41% of patients, respectively, were vaccinated; 1, 2, and 3 vaccinations were received by 60, 57, and 285 patients, respectively; 413 were unvaccinated). Compared to unvaccinated patients, the patients vaccinated three times developed the first ARI later (p<0.0001); the relative risk of developing cardiovascular complications (CVC) was 0.88 (95% confidence interval: 0.65-1.10). Among vaccinated patients, there were fewer patients with ARI (p<0.001) and cardiovascular diseases (p=0.02) not only in summer compared to winter, but also in summer, ARI developed in 41.2% fewer patients than in unvaccinated (p=0.002).

Conclusion The use of two analytical methods allowed us to identify additionally both non-specific and persistent specific effects of three-year flu immunization in cardiological patients in summer, which needs to be confirmed in randomized placebo-controlled studies.

Keywords Regular annular vaccination; flu; secondary prevention of cardiovascular complications; cardio vascular events; self-controlled case series method

For citations Platonova E.V., Gorbunov V.M., Koshelyaevskaya Ya.N., Nazarova O.A., Belova O.A., Furman N.V. et al. Repeated Annual Seasonal Influenza Vaccination of Patients With Circulatory Disease as Secondary Prevention of Cardiovascular Events: an Additional Self-Controlled Case Series Analysis. Kardiologiia. 2025;65(7):17–27. [Russian: Платонова Е.В., Горбунов В.М., Кошеляевская Я.Н., Назарова О.А., Белова О.А., Фурман Н.В. и др. Регулярная ежегодная вакцинация против сезонного гриппа пациентов с болезнями системы кровообращения как вторичная профилактика сердечно-сосудистых событий: дополнительный анализ методом самоконтролируемой серии случаев. Кардиология. 2025;65(7):17–27].

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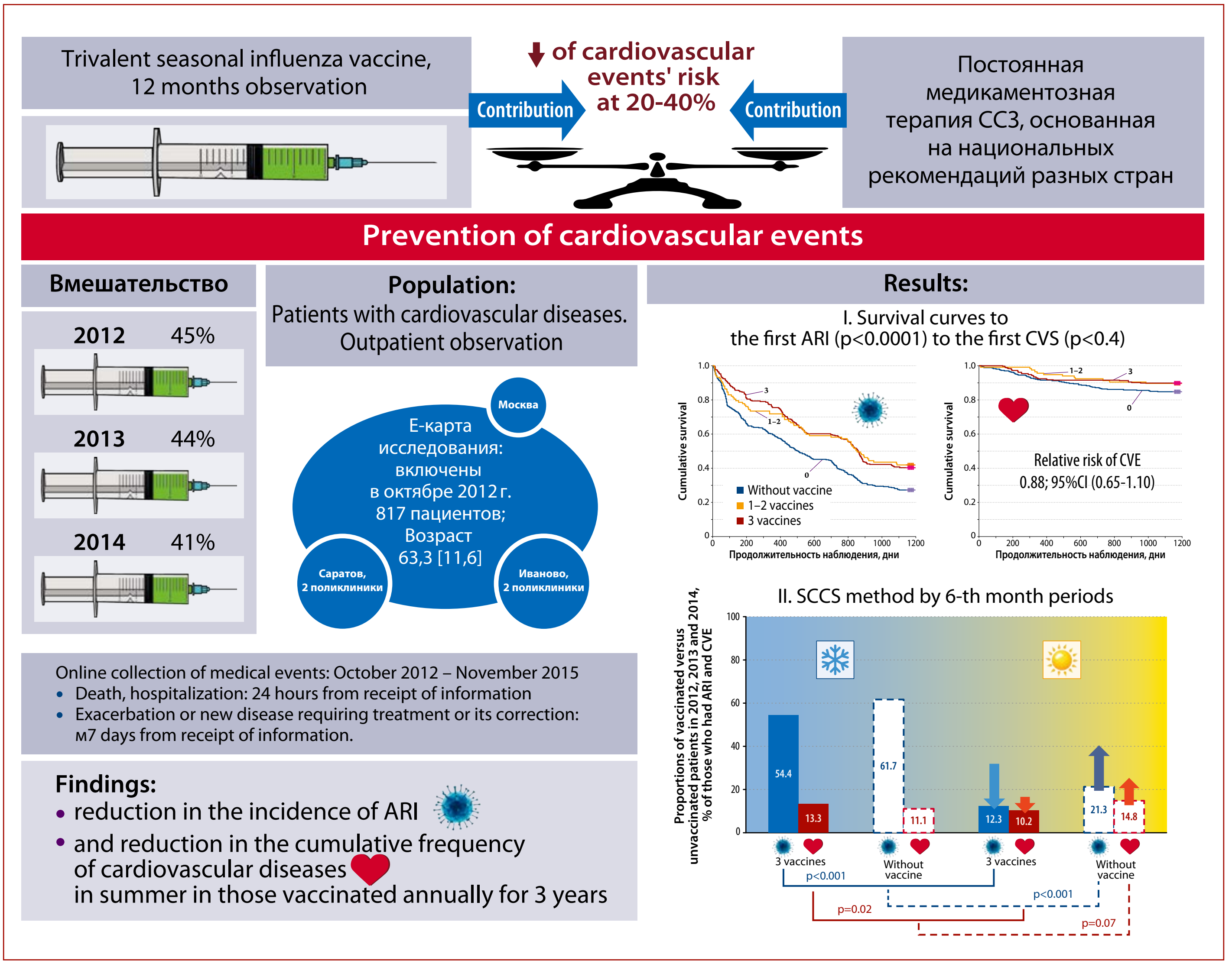
Introduction

The use of influenza vaccine worldwide in patients with cardiovascular disease (CVD) remains insufficient to date [1], despite the role of inflammation atherosclerosis' progression. This situation may be related to the extremely small number of long-term prospective studies of its regular annual use [2].

Nevertheless, experts state that prophylaxis with seasonal influenza vaccine (primary [3] and secondary [4] with intermediate level, tertiary [5-7] with high level of evidence) provides 20-40% reduction in the risk of cardiovascular events (CVE) [2]. This contribution of immune prophylaxis is comparable in its impact on prognosis to the use of continuous preventive thera-

Central illustration. Repeated Annual Seasonal Influenza Vaccination of Patients With Circulatory Diseasвe as Secondary Prevention of Cardiovascular Events: an Additional Self-Controlled Case Series Analysis



py for CVD approved by national guidelines from different countries [1]. However, two peculiarities in vaccine studies should be noted. The first one is related to the follow-up period, and the second one is related to the principle of analysis.

1. Recommendations for the use of seasonal influenza vaccine in cardiac patients are based on a 12-month follow-up after a single immunization [8]. This time limitation is determined by the seasonal nature of the infection and, consequently, the seasonal assessment of the vaccine effect. To date, there is only one theoretical model for estimating vaccine efficacy over two seasons that takes into account the complexities of laboratory analysis in such studies [9]. Due to this limitation of laboratory evaluation of vaccine effect, only clinical outcomes are considered as validating criteria for influenza vaccination efficacy in long-term prospective studies [10].
2. Vaccination efficacy is determined by a single statistical method. For prospective design, the traditional approach is to analyze the comparison of event occurrence (log-rank test), cumulative incidence (Kaplan-Meier method), and risk of events with 95% confidence interval (CI) (Cox proportional hazards model) over 12 months of follow-up [4-7]. The self-controlled case series method is used for retrospective design [3, 11-13].
3. The prospective design assumes that the data have a normal distribution typical of chronic non-communicable diseases, while the retrospective design assumes a Poisson distribution typical of seasonal infectious diseases. Thus, when analyzing morbidity with different distributions, using only one approach will probably not provide a complete assessment of vaccination efficacy. We provided to re-analyze the data from a prospective study [14] with a comprehensive sequential use of survival curves and the self-controlled case series method.

ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2820

Objective

To study additional information on the effect of annual seasonal influenza vaccination for 3 years on the risk of acute respiratory infection (ARI) and CVE in cardiac patients under outpatient observation using this approach.

Material and Methods

A total of 817 patients were enrolled in a multicenter prospective open comparative study by physicians from four polyclinics coordinated by regional centers from October 01, 2012 to November 12, 2012 [14]. All participants had a history of CVD and were registered at the outpatient clinics at their place of residence in Ivanovo and Saratov. A total of 4 consecutive annual seasonal influenza vaccinations were performed in the intervention group from October 01, 2012 to November 2015 in Saratov and 3 in Ivanovo (from October 10, 2012 to November 2014). Inactivated trivalent vaccine Grippol Plus with a topical set of influenza A (H1N1), A (H3N2) and B virus strains for each season (SPA "Petrovax Pharm", Russia) was used. One immunizing dose of 0.5 ml contains at least 5/5/5 µg of hemagglutinin of subtypes A (H1N1 and H3N2) and type B produced by "Abbott Biologicals BV" (Netherlands) and immunoadjuvant Polioxidonium® 500 µg in phosphate-salt buffer. The analysis included the period from October 01, 2012, to October 30, 2015, with online collection of events according to predefined rules. One protocol was used throughout the study to enter information into a single electronic registration card: deaths and hospitalizations (within 24 h of receipt of information); the therapy' correction due to worsening of the current disease or emergence of a new disease requiring treatment (within 7 days of receipt of information). Medical information for analysis was coded using ICD-10. The class "Diseases of the circulatory system"(I00-I99) was categorized as CVE. Prevention of ARI cases was considered specific, cases of CVE and other chronic non-communicable diseases (CNCDs) were considered nonspecific effects of vaccination. The study was approved by the independent ethical committees of FGBU "GNICPM" of the Ministry of Health and Social Development of the Russian Federation (meeting protocol No. 08–07/12 of 18.09.2012), FGBU "SarNRCC" of the Ministry of Health and Social Development of the Russian Federation (meeting protocol No. 6/2 of 12.09.2012), RBHI CD (meeting protocol No. 10 of 28.09.2012). All study participants signed informed consent to participate in the study.

Statistical analysis

Descriptive statistics methods (mean, standard deviation, minimum, maximum), analysis of observed event frequencies (χ^2), and survival analysis were applied for data processing. Calculation was performed using SPSS software (v.23). Differences at $p<0.05$ were considered statistically significant.

Construction of survival curves was used to assess differences in the time of onset of the first event in patients immunized 0, 1-2 and 3 times.

The self-controlled case series (SCCS) method was modified due to the relatively small number of observations. The cumulative frequency of events was estimated by comparing their occurrence in the 6-month "risk" period after vaccination (cold season: October-March), and the "baseline" 6-month period (warm season: April-September) preceding the next vaccination, cumulatively in three seasons in each patient vaccinated 0, 1-2, and 3 times. Each patient was a self comparison pair. After personal intraindividual analysis, the results were summarized. For objectivity, the summarized data were compared again for the same periods but between vaccinated and unvaccinated study participants. A result was considered reliable if there was agreement with the initial assessment of differences in the summarized data.

Eight variations in actual vaccination status over the 3 seasons were taken into account, as program participants could: 1) change their willingness to be vaccinated or not, and 2) have contraindications at the time of the next vaccination.

Results

Validated data from 813 patients were analyzed. The general characteristics of the study participants are summarized in Table 1.

Table 1. Characteristics of study participants

Index	value
Mean age, years(M±SD)	63,3±11,6
male,%	40,5
Medical history, %	
AH	92
MI	24
HF	12
Stroke	1
Vaccination coverage, %	
2012/2013	45
2013/2014	44
2014/2015	41

AH – arterial hypertension; MI – myocardial infarct; HF – heart failure.

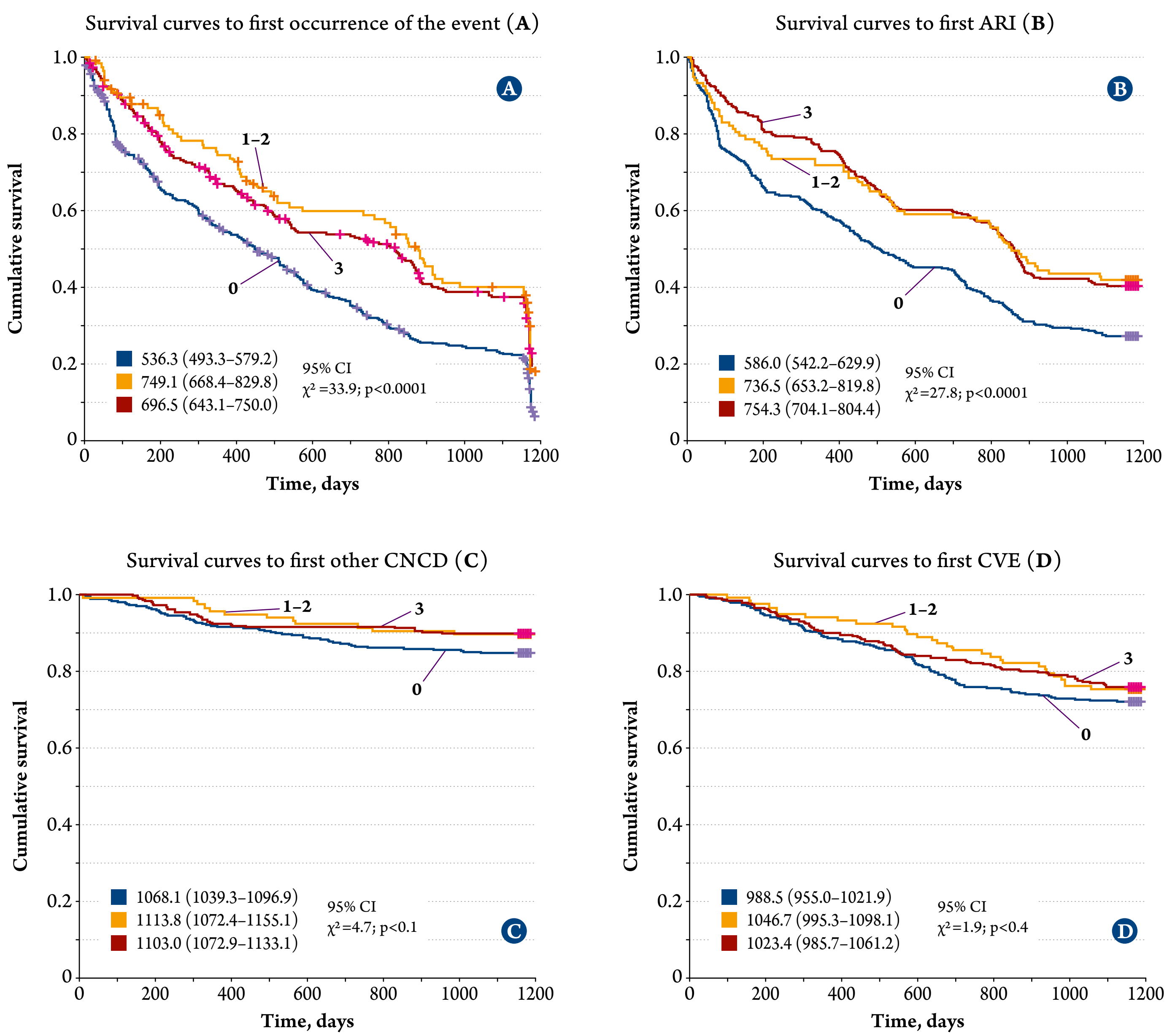
Four hundred and thirteen patients were not vaccinated during the 3 seasons; 60, 57, and 285 participants received 1, 2, and 3 vaccinations during this period, respectively. During the follow-up period from October 2012 to November 2015, all events (n=1319) identified by physicians were categorized into 3 groups:

1) CVE, n=262;
2) other CNCDs, n=160; and
3) ARI, n=897. Table 2 summarizes all variants of diagnoses recorded during the study.

Data from patients (n=620) with all occurring first events, including those with deaths (n=33) and hospitalizations (n=160), were considered together. In Figure 1, the graphs demonstrate the difference in the divergence of the curves summarized for all first illnesses (A), for first ARIs (B), first other CNCDs (C) and first CVE (D). Over the three-year follow-up period, the event occurred on average earlier among unvaccinated patients than among vaccinated participants. These patterns were statistically significant for all first events as well as for the first ARI cases (see Figure 1, B).

The difference morbidity events were found among unvaccinated, regularly and occasionally vaccinated participants during the 3 years of follow-

Figure 1. Survival curves describe all cases (**A**) and separately ARI (**B**), other chronic non-communicable diseases (**C**), cardiovascular event (**D**) up to the first event for 3 seasonal vaccinations against influenza from 2012/2013 to 2014/2015 inclusive



The first event time is presented as mean in days with 95% confidence interval (CI). 0 – blue curve; patients without immunization; 1–2 – yellow curve, patients with one or two vaccinations; 3 – red curve, patients with three vaccinations. + – censored data for 0, 1–2, 3 curves.

ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2820

Table 2. New diseases and worsening of existing diseases registered during the observation period (2012–2015)

	Nosology		
	Diseases of the circulatory system	**Other chronic non-communicable diseases**	**ARI***
ICD-10 code	I10, I11, I11.0, I11.9, I15, I15.8, I20.0, I20.8, I20.9, I21, I21.9, I27.9, I46.1, I48, I49.0, I49.5, I50, I50.1, I50.9, I63, I63.8, I63.9, I64, I67, I67.8, I67.9, I69 R96.1 I70	E10, E11 J40.0, J41, J42, J44.0, J44.9, J45, J45.9 K25, K29, K29.7, K35, K70, K80, K80.1, K85, K86.1 M05, M10, M13, M15, M16, M17, M19, M19.9, M24.1, M40, M42, M42.0, M48.1, M81.1 N11.0, N20, N30, N30.0, N30.9, N60, N64, N77.1, N76.0, N85	J06, J06.8, J22, J04, J01, J02, J03, J18, J20, B02,9

* – diagnoses J10 were coded in J06.8 due to lack of laboratory verification. DCS – diseases of the circulatory system; other NCDs – other chronic non-communicable diseases; ARI – acute respiratory infections

up (82.3, 70.2, and 68.4%, respectively; χ^2-square 18.1; p<0.0001; see Figure 1, A). However, the rate of the three nosological groups was not differed for each curve, reflecting data from patients without vaccination, with 3 and 1-2 vaccinations. (73.8, 15.6 and 10.6%; 76.0, 17.0 and 7.0%; 81.3, 11.3 and 7.5% for ARI, CVE and other CNCDs, respectively; χ^2-square 3.74; p=0.44; see Figure 1, A).

The use of vaccination in addition to standard CV therapy resulted in a 12% reduction in the relative risk of developing CVE (Table 3), but was statistically insignificant.

Thus, this method of analysis confirmed the specific effect of regular vaccination over 3 years, whereas the nonspecific effect was inconclusive. Since the survival curves reflected the occurrence of only the first events and did not allow for seasonal incidence, an additional analysis was performed.

Table 3. Estimation of the relative risk of developing cardiovascular events depending on the use of influenza vaccine over 3 years

Investigasion	Patients, n	CVE +	CVE no	HR(95% CI)
Vaccination 1–2 and 3 (total)	117 и 285 (402)	29 и 69 (98)	88 и 216 (304)	0,88(0,69– 1,10)
Without vaccination	413	115	298	

CVE – cardiovascular event; HR – hazard ration; CI - confidence interval

Figure 2. Effect of influenza vaccination on overall "cumulative" incidence over 3 years of observation in two compared periods

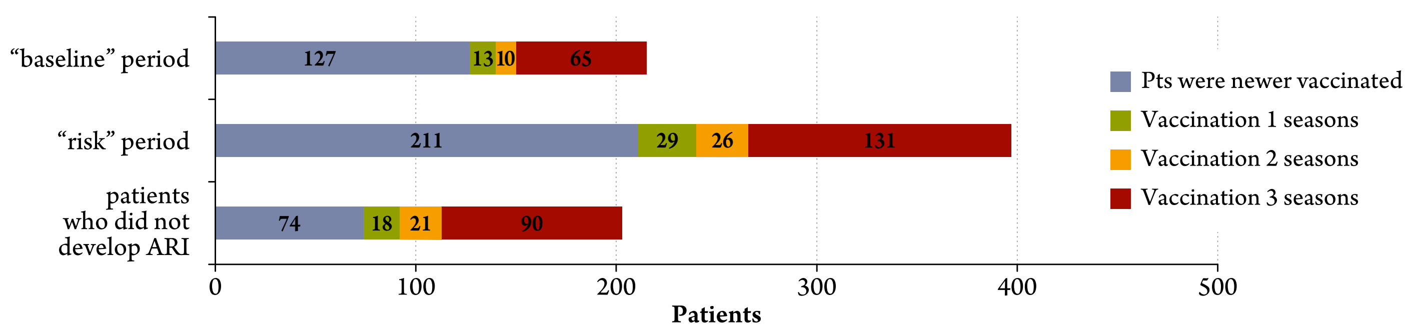


Figure 3. Comparative impact of annual vaccination on the average "burden" of events per patient in the "risk" period versus the "baseline" period for 2012–2015

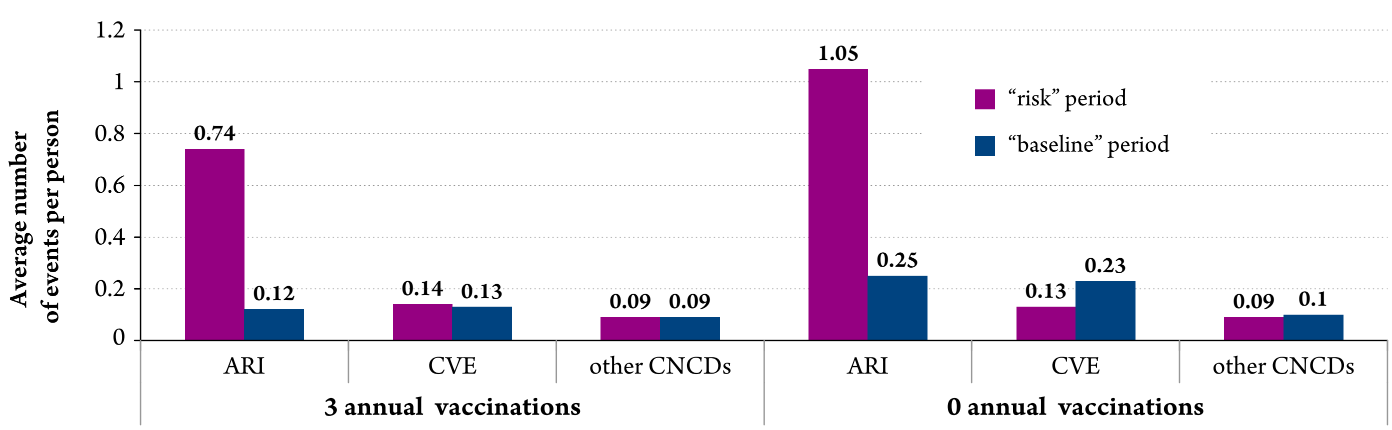


Table 4. Model 1 (n=815): the effect of annual seasonal influenza vaccination in the “risk” period (I) and in the “baseline” period (II) over 3 seasons (1–3 vs. 0 vaccinations)

Annual vaccination during 2012–2015 yy		1–3, n=402	0, n=413	1–3, n=402	0, n=413	p* (I vs. II)		p** (1–3 vs. 0)	
Patients, %	events	I		II		1-3	no	I	II
	ARI	53.3	63.7	11.2	21.5	<0.001	<0.001	0.003	<0.001
	CVE	14.4	13.1	10.2	18.2	0.12	0.04	0.94	0.02
	other NCDs	7.7	7.7	8.5	11.6	0.02	0.07	0.98	0.13

*– SCCS method (each patient is self comparison pair in the “risk” and baseline periods); **– comparison between the intervention and its absence for each period. Significant differences between groups comparisons by p<0.05. ARI – acute respiratory infections; CVE – cardiovascular events; other NCDs – other chronic non-communicable diseases.

Table 5. Model 2 (n=698): the effect of regular annual seasonal influenza vaccination in the “risk” period (I) and in the “base” period (II) over 3 seasons (3 vs. 0 vaccinations)

Annual vaccination during 2012–2015 yy		3, n=283	0, n=413	3, n=283	0, n=413	p* (I vs II)		p** (3 vs 0)	
Patients, %	events	I		II		3	0	I	II
	ARI	54.4	61.7	12.3	21.3	<0.001	<0.001	0.05	0.002
	CVE	13.3	11.1	10.2	14.8	0.02	0.07	0.38	0.08
	other NCDs	7.7	7.5	7.7	10.7	0.88	0.62	0.92	0.19

* – comparison by the SCCS method (is self comparison pair in the “risk” and baseline periods). ** – comparison between the intervention and its absence. Significant differences between the comparison groups at p<0.05. ARI – acute respiratory infections; CVS – cardiovascular events; NCD – chronic non-communicable diseases.

Using the SCCS method, 1095 observation days were presented as two periods. Each period contained the summed number of patients with events over three seasons. Figure 2 clearly shows the seasonal difference in the registered events between the comparison periods we selected by duration depending on vaccination over 3 years.

As expected, ARI cases were more frequent in the “risk” period than in the “baseline” period, regardless of vaccination (Fig. 3). However, among vaccinated patients, the infectious “load” per patient was 1.5 times lower in the "risk" period and 2 times lower in the baseline period than in unvaccinated patients. During the “risk” period, the number of CVE and other CNCDs per patient was comparable in both vaccinated and unvaccinated patients. “Load” of CVE in the baseline period per unvaccinated patient was 2 times higher than in the vaccinated patient.

We analyzed 2 models, considering 8(!) variants participants’ status of the actual vaccine administration over 3 years. In the first model we included all 8 variants, comparing unvaccinated patients (n=413) with patients vaccinated three times or at least once (n=402) (Table 4). In the second model the analysis was restricted to comparing 2 variants: unvaccinated patients (n=413) and triple-vaccinated patients (n=283). Thus, the second model compared patients with permanent intervention status and/or no intervention status (Table 5).

Specific effect

Both models confirmed the specific effect of regular vaccination. Only the second model in the “risk” period described an inconclusive advantage of vaccination over unvaccinated patients (p=0.05 vs. p=0.003, respectively; see Tables 4, 5). The proportion of patients with ARI was lower in the “base” period than in the “risk” period. This observation certainly reflected the seasonal nature of the infection, nevertheless the analysis again showed that regularly vaccinated patients with ARI were 4.4 times fewer in the summer period (12.3% vs. 54.4%; p<0.001), while they were only 2.8 times fewer among the unvaccinated (21.3% vs. 61.7%; p<0.001; see Table 5). In the second comparison, this pattern was

ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2820

maintained. In summer, there were 1.7 times more ARI patients among the unvaccinated than among the regularly immunized patients (21.3% vs. 12.3%; p=0.002; see Table 5).

Nonspecific effect in relation to CVE

The first model showed no differences between cold and warm seasons in vaccinated patients (14.4% vs. 10.2%; p=0.12; Tables 4, 1–3), nor did it distinguish between vaccinated and unvaccinated patients (14.4% vs. 13.1%; p=0.94) in the "risk" period (Table 4). The second model, although it distinguished between vaccinated patients between periods (13.3% vs. 10.2%; p=0.02; Table 5), but the difference disappeared when immunized and unvaccinated patients were compared (13.3% vs. 11.1%; p=0.38) (Table 5). Thus, during the "risk" period, we did not confirm the "direct" nonspecific effect of routine vaccination in immunized patients during 3 years of follow-up.

However, attention was drawn to the statistically significant prevalence of CVE among unvaccinated patients in summer described by the first model (18.2% vs. 13.4%; p=0.04; see Table 4), confirmed by comparison of vaccinated and unvaccinated patients (10.2% vs. 18.2%; p=0.02; Table 4). The second model showed no statistically significant differences in summer in unvaccinated patients (14.8% vs. 11.1%; p=0.07 and 14.8% vs. 10.2%; p=0.08; Table 5).

Thus, the specific effect of regular vaccination was confirmed by both models. Both in the "risk" and in the "baseline" period, there were fewer ARI patients among all vaccinated variants. No convincing evidence for a nonspecific effect in the vaccinated was found. However, the coincidence of the summer prevalence of ARI patients and the increase in the proportion of patients with CVE among the unvaccinated, even in the absence of a significant decrease CVE among the vaccinated, allows us to hypothesize the presence of a nonspecific effect of regular.

Discussion

In the evaluation of vaccination efficacy to date, there are problems limiting the study of regular long-term use of these biological interventions in patients with chronic diseases [15]. An additional factor is analysis dependent on study design. Previously [14], we used a combined endpoint defined as death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke in our survival curve analysis [14]. Compared with unvaccinated patients, vaccinated patients had a 59% lower risk of developing CV complications [14]. In the current publication, the endpoint was redefined in the data analysis. It included all first CVEs. Under this condition, the risk of developing a CVE became only 12% lower in vaccinated compared to non-vaccinated patients. This difference in results can be explained by the fact that the protective properties of influenza vaccine against acute cardiovascular accidents have been shown previously [14], consistent with the results of other investigators [3–7]. In addition, previously [14] only considered the effect of the first vaccination on the outcome, whereas our work considered the effect of three annual vaccinations. Therefore, the weak reduction in the relative risk of CVE could be due to the vaccine-related immune history of our patients, as mentioned previously by J. A. Lewnard and S. Cobey [15]

For objectivity, we supplemented the analysis with the SCCS method [3, 11, 12]. It focuses on immunized patients with CVE endpoints in the "risk" period corresponding to the protective level of immunization. Although limitations need to be considered in its analysis [16, 17], the method had an advantage over survival curves because it was developed for values with a Poisson distribution and was originally applied to assess vaccine safety [18]. The choice of this method was also related to the results of studies of tertiary prevention of CV complications, in which experts voiced the hypothesis of a nonspecific effect of the influenza vaccine [2, 19]. It is extremely difficult to distinguish it from the specific effect of the vaccine, but focusing on the period free of seasonal ARI, it is possible to assume [20].

In addition, the use of double comparisons reduced analysis bias because each participant was not solely a control for themselves. The initial prospective design provided pairwise comparisons of the intervention group and the group without immunization in each period, respectively. The former (generalized) model, in contrast to the latter (restricted to patients with a history of regular vaccination), showed a significant reduction in the number of patients with ARI. The explanation may be the 1.4-fold reduction in sample size of the second model with regular annual immunization and 100% post-vaccination history of these patients, the mechanism of which is explained by the theory of D. J. Smith et al. [9]. With regard to CVE and other CNCDs in the three-year " risk" period, no intervention model showed statistically significant differences between the vaccination and comparison groups. This distinguished it from data from a five-year follow-up in which it was shown that the risk of CVE in the first six months was lower in vaccinated patients than in unvaccinated patients (9% vs. 13.5%; p=0.045) [21].

Baseline period

Continuation of the specific effect was shown by both models: compared to unvaccinated patients, the proportion of vaccinated patients with ARI was 1.9 and 1.7 times lower (p<0.001 in both cases). With regard to the nonspecific effect, only the first model showed not only an increase in the proportion of unvaccinated patients with ARI (p=0.04), but also its almost two-fold excess compared to vaccinated patients (p=0.02). The second model recorded a decrease in the proportion of patients with CVE (p=0.02) among vaccinated patients without statistically significant differences with unvaccinated patients (p=0.08). Thus, the first model confirmed the increased "burden" of CVE during the baseline period in the absence of regular vaccination, repeating the previous analysis [21]. In this regard, only a probable nonspecific effect can be assumed.

In contrast to the "risk" period, we observed good "reproducibility" of the baseline period data in two different analyses (current and follow-up, which included four annual vaccinations [21]). Thus, the SCCS method complemented the analysis of the survival curves. While lack of immunization led to an increase in the incidence of ARI during the warm season, there was a decrease in the proportion of ARI patients during this time period among those who were regularly immunized. This pattern indicated a continuation of the specific effect of regular annual influenza vaccination. The increase in the proportion of patients with ARI among the unvaccinated in summer and the tendency for a decrease in the proportion of patients with ARI among the vaccinated during this period do not allow us to exclude a nonspecific effect of annual immunization against seasonal influenza. During the "risk" period, the nonspecific effect of regular three-year vaccination did not differ between the groups.

In contrast to the "risk" intervals of 3, 7, 14, 28, and 90 days [11, 12] and 120 days [3], we used a 180-day period equal to the time period for assessing vaccine immunogenicity that we described earlier [22]. This time interval is considered to correspond to the end of the peak of vaccine action [10]. According to our data, in patients vaccinated three times annually, the levels of post-vaccination and pre-vaccination antibody titers were equalized over a 180-day period. Thrice-vaccinated patients did not have the high antibody titer levels [22] that they had after the first vaccination [23]. But it was in regularly vaccinated patients that the difference in seroconversion levels between the third and first vaccinations had a small spread, in contrast to that in unvaccinated patients, who had a similar delta with a very large spread (at the expense of those who had not had influenza and those who had had influenza) [22]. It is possible that regular influenza immunization altered B-cell activity and influenced their interaction with CD4+ T-lymphocytes, leading to a decrease in pro-inflammatory cytokines [24]. We attributed the decrease in the number of CVEs (although not significant, possibly due to only 40% vaccination coverage) and ARIs in vaccinated patients compared to unvaccinated patients in the baseline period to the effect of regular immunization, which is responsible for the specific dynamics of seroconversion [22].

Clinically, our results repeat the results obtained by other researchers. The authors [1, 20] drew attention to the data of well-known works [4–7]. They indicated that in addition to an approximately 30% reduction in the incidence of acute CVE in vaccinated versus unvaccinated patients, vaccination was also effective in preventing cardiovascular complications during the summer season, a period in which influenza virus circulation is usually absent. According to the authors [1, 20], this observation allowed us to put forward a new mechanistic hypothesis of a direct protective effect of influenza vaccination on the inflammatory process associated with the stabilization of atheromatous plaques.

Authors of preclinical [25] and clinical studies [3, 19] have also raised the issue that influenza vaccination may represent more than protection against influenza. The results of studies [5–7, 19, 25, 26] suggest a nonspecific effect of the vaccine. This effect is most expected in the setting of specific inflammation in patients with acute coronary syndrome, especially without ST-segment elevation [27], with a characteristically worse course of atherosclerosis in the mid- to long-term prognosis [28–30]. For example, influenza immunization not in the vaccination season but in a 72-hour window after selective coronary angiography or percutaneous coronary intervention was associated with a significantly greater reduction in the risk of adverse MACE in myocardial infarction without ST-segment elevation than in ST-segment elevation infarction [31]. The authors [7, 19] supported the assumption that influenza vaccine may have a direct atheroprotective effect through direct cross-reaction of antibodies to hemagglutinin HA1 of influenza virus with candidates for the role of cross-reacting proteins: apolipoprotein B (ApoB) [25] and bradykinin B2 receptor (BKB2R) [26]. But this mechanism has not been definitively studied [20].

ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2820

Thus, summarizing the results of our study and the data of other authors, in addition to the well-known specific effect, we can assume the existence of several nonspecific effects of inactivated influenza vaccine. Thanks to the SCCS method it was possible to show the continuation of the specific effect in the warm season, to assume that the specific effect of regular influenza vaccination can be well reproducible, and to assume in this period the nonspecific effect of regular seasonal vaccination for 3 years. Off-season administration of such a vaccine causes a nonspecific effect, probably with a different mechanism of action, improving the medium- and long-term prognosis in the treatment of patients with non-ST-segment elevation myocardial infarction [2, 7, 31–33].

Limitations of the study

The following factors influenced the outcome of the analysis in our program: lack of randomization; difficulty in comparing patients who received different numbers of vaccinations.

Conclusion

Reduced incidence of acute respiratory infection in cardiac patients repeatedly vaccinated against seasonal influenza over 3 years was demonstrated by sequential application of two methods of analysis. The self-controlled case series method in the setting of regular annual vaccination revealed a pattern of reduced cumulative incidence of cardiovascular events during the warm season. The association of this finding with a persistent specific effect of immunization deserves special attention. Its confirmation in longer randomized trials will answer the question of how many seasonal immunizations a cardiac patient should receive to achieve a nonspecific anti-inflammatory effect of regular administration of inactivated trivalent seasonal influenza vaccine as part of secondary prevention of cardiovascular complications in addition to conventional pharmacotherapy.

Acknowledgments

The authors express their deep gratitude to their colleagues – the management and physicians of polyclinics of the cities of Ivanovo and Saratov, without whose participation the writing of this article would not have been possible.

Funding

The article was prepared on the basis of the materials of the study performed in 2012–2016 with the support of "SPA Petrovax Pharm".

Conflict of interest

The authors' position, which may differ from the position of "Petrovax Pharm", is stated in the article.

The article was received on 20/11/2024

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