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## Cost-Effectiveness Of Intranasal Interferon Gamma For Inpatient Treatment Of Influenza

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### ABSTRACT

Influenza is one of the most prevalent and socially significant upper respiratory tract infections. The majority of patients suffer from its mild form; medium and severe forms of the disease may be associated with complications, and hospitalization is often required for such patients. The pharmacoeconomic evaluation demonstrated the benefit of the use of intranasal recombinant interferon gamma (Ingaron) in a combined therapy of influenza in hospital. The inclusion of Ingaron into the therapy of influenza reduces the duration of the disease and the length of hospital stay. The economic effect of the administration of Ingaron includes budget savings for the health care system of Russia and improved life quality of patients.

**Keywords:** interferon gamma, influenza, QALY, budget impact.

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## INTRODUCTION

The morbidity from influenza in 2018 in Russia was 26.33 per 100,000 persons (24.5% lower compared to 34.86 per 100,000 in 2017); 113.90 per 100,000 children age 1-2; and 93.91 per 100,000 children age 3-6 according to Rospotrebnadzor. [1] Biomolecular analyses showed that 49.58% of influenza cases were caused by A(H1N1)pdm09 subtype of virus; 25.7% by A(H3N2) subtype; and 24.7% by B subtype. The disease can be both mild and severe, and sometimes leads to death. In 2018, 127 lethal cases of influenza were registered (2.7 times higher than 46 cases in 2017), including 14 cases in children younger than 17 years of age (13 cases in 2017). Influenza caused by A(H1N1)pdm09 virus prevailed in these fatal cases.

Hospitalization and death generally occurs in high-risk groups. The WHO estimates that influenza epidemics account for 3-5 million severe cases of the disease and 290,000–650,000 deaths from respiratory diseases annually.

Official data provided by Rospotrebnadzor [1] show that influenza occupies 12th place among contagious diseases in respect of economic burden, and it cost more than 1,096,935,000 RUB of economic losses in the season 2018-2019. Although vaccination is an effective preventive measure against influenza, it does not fully eliminate the possibility of its development. The treatment includes specific antiviral and symptomatic options. [2,3] Effective budget planning in the health care system requires evaluation of cost-effectiveness of particular therapies of influenza. Recombinant interferon gamma (IFN-gamma) for intranasal administration (Ingaron) has been registered for the treatment of influenza in a combined therapy. Its effectiveness in the treatment and prevention of influenza was proved in controlled clinical studies [4-6].

## MATERIALS AND METHODS

The aim of the study was to perform a pharmacoeconomic analysis of interferon gamma in a combined therapy of influenza in patients hospitalized due to clinical indications. The analysis was based on the results of an open comparative evaluation of the effectiveness and safety of IFN-gamma (INGA 2018). [6]

### Experimental design

A decision tree with a node of strategy selection (administration of the studied drug vs. standard therapy) and two branches of possible outcomes was used. The tree did not have a probabilistic component.

### Experimental stages

On the first stage, the impact of the addition of IFN-gamma to the therapy of influenza on the health care budget was evaluated. The cost of treatment with the drug was compared with the resulting reduction of the length of hospital stay. Clinical data were obtained from the randomized comparative study of effectiveness and safety of interferon gamma (lyophilizate for solution for intranasal administration) in a combined therapy of adults with moderate and severe influenza (INGA 2018). [6] The cost of hospital stay was calculated based on the general tariff agreement for Saint Petersburg in 2019 [7] ('Hospitalization with influenza and acute respiratory viral infections', code 211500). According to this tariff, the average cost of one day in hospital was 4365.9 RUB. The study did not register any adverse effects associated with IFN-gamma, and the baseline therapy was identical; therefore, it was assumed that the spending values differ only in respect of the cost of IFN-gamma. The cost of therapy was calculated from the registered price on the List of Vital and Essential Drugs (<http://grls.rosminzdrav.ru>), which was 236.25 RUB for a pack with 1 flask of lyophilizate for the solution for intranasal administration containing 100,000 ME of recombinant human interferon gamma. In the clinical study, 2-3 drops of recombinant human interferon gamma (Ingaron) were administered to each nasal passage 5 times a day for 5 days. One drop contained 0.05 ml of the solution, and the course required one flask of the drug.

### Experimental conditions

The cost included VAT and maximal wholesale markup specified in the Decree of the Government of Saint Petersburg of 6 September 2010 no. 1190 'On the markups for vital and essential drugs'.

The number of patients, who may require the treatment with recombinant human interferon gamma (Ingaron), was assessed based on the data on influenza morbidity in Russia in January—May 2019.

The difference in losses of life quality due to the therapy with and without IFN-gamma was evaluated to assess the overall effectiveness of the drug. The reduction of hospital stay by 1.25 days was the main result, so it was assumed that patients left hospital in their full health and gained 1.25 quality-adjusted life days. In hospital, the condition of patients improved faster in the IFN-gamma group compared to the control group; in order to take this fact into account, the influence on life quality was assessed using EQ-5D instrument. [8] It was noted that intoxication had the greatest impact on life quality, therefore the deterioration of life quality due to this factor was assessed, and the resulting weighting coefficients were used in the analysis. The share of intoxicated persons was compared to the weighting coefficient of life quality (it was assumed that persons without intoxication have full life quality, and the sum total was equal to one). Life quality after 5 days of hospital stay was assessed based on the assumption that there is some anxiety and restriction of normal activity until discharge.

To calculate net monetary benefit (NMB), added QALY was converted into monetary equivalents based on the willingness-to-pay threshold of 3 GDP per capita. The GDP per capita was 707,601 RUB according to the website of the Federal State Statistics Service of Russia (<http://www.gks.ru>).

### Experimental instruments

Discounting was not performed due to a short time horizon of the study. Calculations were completed using Microsoft Excel.

## RESULTS AND DISCUSSION

The strategy with administration of IFN-gamma was dominant compared to the standard therapy, because the cost of hospitalization was lower; the cost of one day in hospital (4365.90 RUB) was almost 15 times higher than the cost of the considered therapy; no additional adverse reactions were noted; and life quality improved due to an earlier return to full health and relieve of intoxication. The main results of pharmacoeconomic analysis are shown in Table 1.

**Table 1: The results of pharmacoeconomic analysis of the addition of IFN-gamma to the standard therapy of moderate and severe influenza.**

| Parameter  | Standard therapy | Standard therapy + IFN-gamma |
|--|------------------|------------------------------|
| Length of hospital stay, days  | 7.56             | 6.31                         |
| Cost of additional therapy, RUB  |                  | 298.86                       |
| Decrease in cost of hospitalization, RUB   |                  | 5,457.38                     |
| Decrease in total costs per hospitalization, RUB   |                  | 5,158.52                     |
| Quality-adjusted life days in the period of hospitalization (considering intoxication)         | 6.379            | 6.073                        |
| Quality-adjusted life gained with consideration of earlier discharge                           |                  | 0.307                        |
| Total financial benefit with consideration of willingness-to-pay threshold per hospitalization |                  | 6,941.50                     |

The table shows that the strategy of administration of IFN-gamma reduced the costs for the health care system (5,158.52RUB in average) and increased life quality by 0.3 days (0.0008 QALY). These numbers may seem negligible in absolute terms; however, more than 16,000 persons suffer from influenza and require hospitalization annually (see below), which results in almost 13 saved QALYs each year. Also, these numbers may be underestimated. For example, a study by Sander et al. on the drug therapy of influenza with oseltamivir, which showed that the addition of this drug reduced the length of hospital stay by 16% (0.95 days of quality life), included effects after discharge in the general evaluation. [9]

Total NMB of the administration of IFN-gamma in this study was 6,941.50RUB and included the direct benefit described above and the monetary evaluation of increased quality-adjusted life based on the willingness-to-pay threshold.

The confidence interval of the change of hospital stay was calculated as a part of sensitivity analysis, and the costs for health care system were evaluated on the higher and lower limits of the interval. It was found that the costs for health care system reduced by 2,385.68 RUB on the lower limit (hospitalization reduced by 0.61 days), and by 7,931.36 RUB on the higher limit. Therefore, the sensitivity analysis showed the robustness of the conclusion that the strategy with the administration of IFN-gamma was dominant compared to the standard treatment.

To evaluate the impact of the addition of IFN-gamma to the therapy of moderate and severe influenza in hospitalized adults on the budget of the Russian Federation, the number of hospitalizations was analyzed based on the data by A.A.Smorodintsev Research Institute of Influenza.<sup>1</sup> It was found that 16,198 in persons were hospitalized within 20 weeks of 2019 in Russian cities and this data formed basis for evaluation.

According to the 'Criteria for the calculation of reserves of preventive and therapeutic drugs, instruments, personal protective equipment and disinfectant agents in the federal subject of the Russian Federation for the period of influenza pandemic' (guidelines MP 3.1.2.0139-18) [10], 50% of total number of hospitalized persons are minors under 18 years old. The respective multiplier was used to establish the impact of the inclusion of IFN-gamma into the standard therapy of influenza in hospitalized adults.

The results of the budget impact analysis and their sensitivity to the changes of the extent of the use of IFN-gamma in hospitalized adults are shown in Table 2.

**Table 2: The results of the evaluation of budget impact of the inclusion of IFN-gamma into the influenza treatment regimen in hospitalized adults.**

| Extent of administration, share of hospitalized patients | Budget savings, thousands RUB |                   |                    |
|--|-------------------------------|-------------------|--------------------|
|  | Baseline parameters           | Lower limit of CI | Higher limit of CI |
| 1  | 41,778.84                     | 19,321.63         | 64,236.06          |
| 0.67   | 27,991.83                     | 12,945.49         | 43,038.16          |
| 0.5  | 20,889.42                     | 9,660.81          | 32,118.03          |
| 0.33   | 13,787.02                     | 6,376.14          | 21,197.90          |

CI — confidence interval; see sensitivity analysis of the baseline scenario above in the text.

The use of IFN-gamma reduced the costs of health care system, and overall budget impact came down to budget savings. Table 2 shows that the budget savings would be almost 14,000,000 RUB in an epidemic season even in the most pessimistic scenario (the drug administered to one third of patients with baseline effectiveness). The savings would be 6,400,000 RUB with the effectiveness on the lower limit of the confidence interval, and over 21,000,000 in case of above-average effectiveness. If the drug were used in a half of patients, budget savings would reach 21,000,000 RUB, 10,000,000 RUB, and 32,000,000 RUB, respectively. The administration in two thirds of patients would lead to savings of 2,000,000 RUB, 13,000,000 RUB, and 43,000,000 RUB, respectively. Maximal savings would be 42,000,000 RUB, 19,000,000 RUB, and 64,000,000 RUB, respectively.

### CONCLUSIONS

The administration of IFN-gamma in adults hospitalized with influenza is associated with budget savings for the Russian health care system and improves life quality of patients.

<sup>1</sup>[https://www.influenza.spb.ru/system/epidemic\\_situation/situation\\_on\\_a\\_flu/?year=2019&week=06](https://www.influenza.spb.ru/system/epidemic_situation/situation_on_a_flu/?year=2019&week=06)

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