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Commentary to the article by V.I. Ignatyeva, M.V. Avksentyeva, O.Y. Rebrova, K.V. Gerasimova, I.G. Soldatova, G.A. Asmolova, L.L. Pankratyeva, E.A. Degtyaryeva and D.Y. Ovsyannikov "Clinical economic analysis of RSV infection immune prevention program results for epidemic season of 2012/2013 in Moscow"

Topicality of the issue
The authors touch upon an issue critical for children in neonatality and the first years of life – immune prevention of respiratory syncytial virus (RSV) infection [1]. It not only features severe course in the setting of no evidence-based effective and safe etiotropic therapy, but also lays a heavy disease burden (DB) on the society. DB may be numerically represented with a WHO indicator DALY (disability-adjusted life year). This indicator characterizes the disease burden in years of life in relation to disability. In other words, it is equivalent to losing 1 healthy life year. It is known that DALY (Score/1,000) for RS infection is 67.7, whereas for adenovirus it is 49.7, for herpes – 34.4, for influenza A – 6.8 [2, 3]. RS infection burden is comprised of two main components – high hospitalization frequency in children with RSV and consumption of healthcare resources by children under 2 years of age. At the same time, there are technologies of controlling this medical and social issue – immune prevention of RS infections with monoclonal antibodies. Palivizumab is considered to be such a vaccine. There is evidence (meta-analysis of clinical trials) that immune prevention has reduced mortality more than 4 times in the group of children born before the 32nd gestation week [4].
Prevention of RS infection is a standard practice in children born before the 30th gestation week regardless of the economic development level. Unfortunately, the Russian Federation does not partake in this process (unlike, say, Ecuador), although preservation and rehabilitation of children's health is proclaimed the priority of Russian healthcare. It is reflected in a range of documents and legislative acts: in the Federal Law No. 323-FZ of 21 November 2011of the Russian Federation "On the principles of health protection of citizens of the Russian Federation", which states that the priority of children's health protection is the principle of health protection; in the National strategy of actions in the interests of children for 2012-2017 approved by the Decree No. 761 of 01 June 2012 of the President of the RF; schedules of priority measures on realization of the key provisions of the National strategy of actions in the interests if children for 2012-2017 until 2014 (approved by the Order No. 1916-r of 15 October 2012 of the Government of the RF); the program of RF healthcare development (approved by the Order No. 2511-r of 24.12.2012 of the Government of the RF), which necessitates increase in efficacy of maternity/obstetric service. All the measures stated in these documents are being gradually implemented, including the medical technologies mentioned by the authors of the article – immune prevention of RS infection.

Advantages of the article
The article by V.I. Ignatyeva et al. is set forth according to the traditional scheme of clinical economic analysis (standards of "Clinical economic analysis", general provision of OST 91500.14.0001-2002). The author substantiates topicality of the issue, scientific novelty and practical implications of the work, defines the aim of the study and lists methods of pharmacoepidemiological and clinical economic analysis. The obtained data were statistically manipulated using difference significance criteria. The study involved detailed analysis of palivizumab immune prevention results in Moscow in the season of 2012/2013. The article features detailed calculation of expenses per 1 disability-adjusted life year and proves that the taken measures prevented economic loss due to infantile mortality decrease. The results

demonstrate that use of palivizumab for preventing RS infection ought to be considered clinically and economically sound.

The article is a complete scientific study; it is well illustrated, written in the literary language and is rather readable despite complicated nature of the issue.

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Clinical economic analysis of RSV infection immune prevention program results for epidemic season of 2012/2013 in Moscow

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Introduction. Respiratory syncytial virus (RSV) is one of the main causes of lower respiratory tract infections (LRTI) in infancy. In certain categories of children the risk of development of potentially lethal severe forms of the disease requiring hospitalization, treatment within resuscitation departments and use of artificial pulmonary ventilation is significantly higher than in any other category. Palivizumab is used to prevent RSV infection in such children; its high efficacy and tolerance were proved by numerous clinical trials. The aim of this study is to assess use of palivizumab for preventing the RSV-associated LRTI in children from the groups of high risk of severe course of this pathology from a clinical economic point of view in the course of a regular stage of RSV infection immune prevention program realized in Moscow in the season of 2012/2013. Materials and methods. The study involved detailed analysis of results of LRTI

*immune prevention with palivizumab in a sample of 189 case report forms containing information on the children who had received 3-5 injections of the drug. The estimated number of hospitalizations and deaths in this group of children in the absence of immune prevention was calculated in the model on the basis of results of the previously conducted studies of the RSV-associated LRTI course. The authors also calculated expenses on this group of children in the presence and absence of palivizumab immune prevention, expenses per 1 disability-adjusted life year and averted economic damage due to infantile mortality increase. **Results.** Use of palivizumab in the group under study has possibly prevented 39 hospitalizations, including 13 hospitalizations with medical care rendering at resuscitation and intensive care units, and 1 death. Immune prevention expenses in the group under study equaled to 33,518,514.60 rubles, whereas the estimated expenses in the absence of immune prevention equaled to 1,698,103.90 rubles. Cost effectiveness increment equaled to 461,165.37 rubles per 1 disability-adjusted life year, which is only slightly more than gross domestic product (GDP) per capita in the RF in 2012 (437,476.22 rubles) and significantly lower than the triple GDP per capita (1.3 mn rubles) – the cost-effectiveness threshold recommended by the World Health Organization for application of health preservation technologies. The averted economic damage per preserved life of 1 child equaled to 29,760,927.36 rubles. **Conclusion.** Use of palivizumab for preventing the RSV-associated LRTI ought to be considered clinically and economically sound.*

Keywords: *respiratory syncytial virus, immune prevention, palivizumab, children.*

INTRODUCTION

Respiratory syncytial virus (RSV) is one of the main causes of morbidity in infancy. According to the World Health Organization, RSV is a cause of 4 million deaths of children under 5 years of age all around the world per year [1]. According to the Russian epidemiologic trial, RSV is the main etiologic factor causing hospitalization of children under 2 years of age with lower respiratory tract infections [2].

There is no adequate ethiopathogenetic treatment of RSV; the infected children usually undergo only symptomatic therapy [3].

In most cases RSV infection is relatively mild, although in certain categories of children the risk of development of potentially lethal severe forms of the disease requiring hospitalization, treatment within resuscitation departments and use of artificial pulmonary ventilation (APV) is significantly higher than in any other category. Such risk categories include premature children (gestation age≤35 weeks), children with bronchopulmonary dysplasia (BPD) and hemodynamically significant congenital heart diseases (CHD) [4]. Palivizumab (Synagis) is used to prevent RSV infection in such children in many countries; its high efficacy and tolerance were proved by numerous clinical trials. The Cochrane systematic review issued in 2013 summarized results of randomized clinical trials (RCT) of palivizumab and confirmed that use of this drug statistically significantly decreases the rate of RSV infection hospitalizations among the children from categories of high risk of lower respiratory tract infection (LRTI) development [5]. Earlier systematic review, RCT meta-analysis and cohort trials conducted in 2011 demonstrated that prevention of RSV infection among premature children with gestation age less than 32 weeks statistically significantly reduces total infantile mortality (4.3 times) and rate of RSV infection hospitalizations (2.9 times) [6]. A range of countries organized registers of palivizumab-taking patients (the most prominent – Canadian – contains data of more than 13,000 patients); analysis of such data demonstrates low rates of RSV infection and RSV infection hospitalizations among the vaccinated patients and decrease in the admission rate in comparison with the historical control [7].

In Moscow, the municipal program of RSV infection immune prevention with palivizumab for premature children, children with BPD and CHD was initiated in the season of 2011/2012. 4.6 and 4.8 times lower rates of LRTI and LRTI hospitalizations, respectively, in comparison with the beginning of the epidemic season of acute respiratory viral infections (ARVI) of 2011/2012 (before immunization) were registered at the same time. Hospitalization was not associated with

RSV infection in neither of the 4 patients vaccinated with palivizumab and hospitalized with LRTI. The program also indicated high safety of the drug: no patients had any serious undesirable phenomena [8].

Cost effectiveness of palivizumab use in Russia was assessed by way of modeling [9]; this determines topicality of the trial.

The **aim** of this trial was to conduct clinical economic assessment of palivizumab use for LRTI prevention in children from categories of high risk of severe course of this pathology in the course of the RSV infection immune prevention program realized in Moscow in the season of 2012/2013.

MATERIALS AND METHODS

In the course of the trial, we compared outcomes and expenses per group of children with high risk of severe course of the RSV-associated LRTI in the presence of immune prevention with palivizumab and similar modeled parameters for the same group in the absence of immune prevention program[1]. We calculated the number of prevented deaths and averted economic damage.

In order to analyze immunization program results, we gather data on characteristics of children involved in the RSV-associated LRTI immune prevention program in Moscow in 2012-2013, efficacy and safety of use of drug palivizumab according to a set of criteria. Each child involved in the program had an individually filled record form containing information on the child's condition at discharge from the inpatient hospital after the primary hospitalization and at each moment of palivizumab injection, information on the number of ARVI and ARVI-associated medical care (doctor calls and emergency calls), hospitalizations and reasons of hospitalizations between injections.

For the purpose of this trial, we used the following data of individual record form of the children who had received 3-5 palivizumab injections (189 children in tote, 36% of all the vaccinated children in the season of 2012/2013):
- number of palivizumab injections per child;
- age of the child at the time of each injection;
- concurrent pathology causing higher risk of severe course of the RSV-associated LRTI [bronchopulmonary dysplasia, hemodynamically significant congenital heart diseases (HSCHD)];
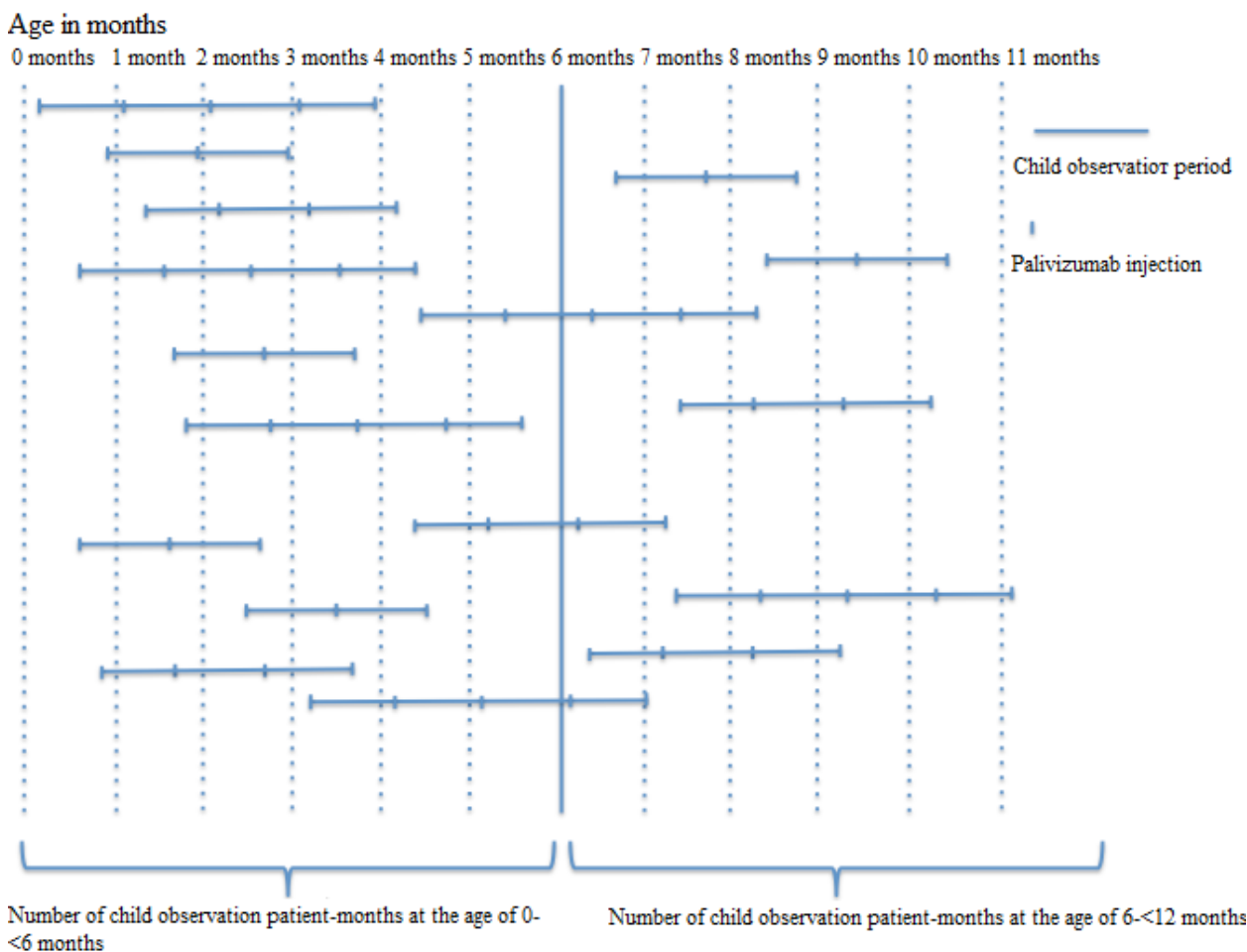- total and RSV-associated number of hospitalizations.

On the basis of the obtained data, we calculated total duration of observation of children involved in the trial in patient-months (pic. 1), rate of BPD and HSCHD and the total number of hospitalizations.

As no representative control group was present at the immune prevention program monitoring, we employed modeling on the basis of data of the earlier studied of the RSV-associated LRTI course in high risk children to conduct clinical economical assessment of the obtained results.

We calculated the estimated number of hospitalizations in the observed group in the absence of immune prevention with palivizumab by multiplying patient-months of observation by risk of the RSV-associated LRTI hospitalization. Risk of the RSV-associated LRTI hospitalization in children with different risk factors of severe course of the disease was determined on the basis of data of a retrospective cohort trial, which involved all children under 3 years of age – members of the Medicaid program in the State of Tennessee in July 1989 – June 1993 (tb. 1); total number of patient-months of observation per epidemic season of RSV infection used to calculate the hospitalization rate equaled to 76,100 [10]. That study was the only one stating the RSV-associated hospitalization rate in a sufficiently extensive group of children with different risk factors of severe course of the disease.

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[1] We used data of immune prevention program results to conduct this trial; we did not form the control group, which is why the control data were modeled.

Pic. 1. Scheme for calculating observation patient-months for children of different age groups.

Age in months

0 months   1 month   2 months   3 months   4 months   5 months   6 months   7 months   8 months   9 months   10 months   11 months

Number of child observation patient-months at the age of 0-<6 months

Number of child observation patient-months at the age of 6-<12 months

Note. Each line corresponds to the period of observation over 1 child; the beginning of the line indicates the moment of the first injection. Number of observation patient-months in each age period was calculated as an aggregate of differences between ages in months at the moment of each injection.

Table 1. RSV-associated LRTI hospitalization risk used for modeling the number of hospitalizations in the absence of immune prevention.

Age	Hospitalization risk depending on the concurrent pathology per 1 observation patient-month		
	BPD	**CHD**	**Prematurity***
0-<6 months	0.0938	0.0201	0.0136
6-<12 months	0.0357	0.0106	0.0066
12-<24 months	0.0122	0.003	0.0020

Note. Calculated according to the data of T.G. Boyce et al. [10]. As their trial [10] featured the hospitalization rate in thousands of patient-years, we converted these values into patient-months. * - calculated on the basis of values (given in the source) for children born on or before the 28th gestation week, from the 29th to the 33rd gestation week and from the 33rd to the 36th gestation week as a ratio of the total number of hospitalizations to the total number of observation patient-years for each age.

As hospitalization risk depends on the child's age (under 6 months of age, 6-12 months of age, over 1 year of age) and concurrent pathology (prematurity, BPD or CHD), the estimated hospitalization rate was calculated separately for each subgroup.

It is known that the admission rate in the Russian Federation is generally higher than in the USA and other economically developed countries due to peculiarities of healthcare system operation.

That is why we introduced a higher admission rate correction coefficient and multiplied it by the estimated number of hospitalizations obtained on the basis of the trial data[2] [10]. The coefficient equaled to the ratio of the total number of hospitalization per 1,000 people in Russian to such a value in the USA according to the publication comparing statistical data on admission rate in the two countries [11].

Rate of medical care rendering to children at resuscitation and intensive care units (RICU) at the RSV-associated LTRI hospitalization was calculated on the basis of the data of 2 RCT studying palivizumab efficacy and safety [12, 13] as the ratio of the registered number of care rendering at RICU to the total registered number of hospitalizations in control groups in the reference trials and equaled to 0.33.

The data on hospital mortality of children with RSV infection are extremely limited, whereas the available values vary significantly [14]. In order to perform our calculations, we used weighted average mortality values obtained as a result of systematic review of 34 trials assessing rate of lethal outcomes depending on the presence of concurrent pathology (prematurity, BPD and CHD) in infants hospitalized due to severe course of the RSV-associated LRTI [15].

The parameters used for modeling outcomes and information sources are given in tb. 2.

Table 2. Values of parameters used for modeling outcomes in the studied group of children with high risk of severe course of the RSV-associated LRTI in the absence of immune prevention.

No.	Parameters used for modeling	Value	Source
1.	Correction coefficient for the number of hospitalizations	1.89	On the basis of the data from [10]
2.	Frequency of care rendering at RICU (from the total number of hospitalizations)	33%	On the basis of the data from [12, 13]
3.	RSV-associated LRTI mortality in the setting of BPD	3.1%	[15]
4.	RSV-associated LRTI mortality in the setting of CHD	53%	[15]
5.	RSV-associated LRTI mortality in the setting of prematurity	1.1%	[15]

Note. RSV – respiratory syncytial virus, LRTI – lower respiratory tract infections, RICU – resuscitation and intensive care unit, BPD – bronchopulmonary dysplasia, CHD – congenital heart disease.

Immune prevention program expenses were calculated as the total palivizumab expenses and additional doctor's appointments due to implementation of immune prevention.

Palivizumab expenses were calculated as multiplication of the number of children in the group under study by the average consumption of 50 ml drug phials per child (the calculated rate throughout the program involving 530 children equaled to 4.2 phials) by purchase cost of 1 phial in the framework of the Moscow program (42,085.11 rubles).

Given that each drug injection required 1 additional doctor's appointment, the number of additional appointments was taken equal to the number of injections.

Medical care expenses were calculated according to the obligatory medical insurance system tariffs applicable in Moscow in 2012 using the correction coefficient equal to 1.96[3] to assess budgetary component in the territorial state guarantees program expenses [16].

The last stage consisted of calculation of cost effectiveness increment as the ratio of expenses differences in the absence and the presence of immune prevention to the number of disability-adjusted life years. The number of disability-adjusted life years was determine on the basis of the calculated number of lethal outcomes at the RSV-associated LRTI in the absence of immune

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[2] The result was rounded to the nearest whole number.

[3] The coefficient was calculated on the basis of data on the authorized cost of the territorial state guarantees program of rendering free medical care to citizens of the Russian Federation according to its financial provision sources in Moscow in 2012 [17].

prevention and the estimated life expectancy at birth in Russia according to the Federal State Statistics Service [17].

We also calculated economic loss due to the RSV-associated LRTI mortality according to the "Method of calculating economic loss due to mortality, morbidity and incapacitation of population" approved by the joint Order of the Ministry of Economic Development of the RF, the Ministry of Health of the RF, the Ministry of Finance of the RF and the Federal State Statistics Service [18].

The age period of economic activity taken was 15-72 years; we did not prognosticate parameters of future years, but took them equal to the corresponding values of 2012 or the nearest year with the available data.

We used population employment data of 2011 [19] due to lack of newer information. Mortality tables for 2010 [20] were used as a source of information on life expectancy at a different age due to lack of newer information.

RESULTS

Characteristics of the population under study and program results of the immune prevention with palivizumab

530 risk group children were vaccinated in Moscow from 01 October 2012 to 01 May 2013 (6 months): premature children (born before the 35th gestation week), children with HSCHD and BPD. CHD were diagnosed in 216 children (40.8%), BPD – in 199 children (37.5%). 40% of children received ≥3 drug injections.

The prevention was conducted on the basis of 10 medical establishments (spread of vaccinated children by medical establishments is given in tb. 3).

Table 3. Number of children vaccinated at various medical establishments of Moscow in the epidemic season of 2012/2013.

Medical establishment	Number of children	
	Absolute	%
Municipal clinical hospital No. 67	189	35.7
Children's infectious diseases clinical hospital No. 6	74	14.0
Filatov children's municipal clinical hospital No. 13	57	10.8
Municipal clinical hospital No. 70	56	10.6
Municipal clinical hospital No. 8	44	8.3
Municipal clinical hospital No. 7	43	8.1
Municipal clinical hospital No. 13	23	4.3
Tushino children's municipal hospital	19	3.6
Morozov children's municipal clinical hospital	14	2.6
Center of family planning and reproduction	11	2.1
Total	**530**	**100.0**

Detailed analysis of vaccination results (by September 2013) was performed in the sample of 189 record forms containing information about the children who had received 3-5 drug injections. 693 palivizumab injections were made in that group in tote: 49.7% of children received 3 injections, 33.9% - 4 injections, 16.4% - 5 injections.

95 (50%) children of the sample were diagnosed with BPD, 68 (36%) – with CHD, 26 (14%) – with prematurity only. The average age of the children at the first injection was 4.1 months, median – 3 [1.1; 5.5][4] months. The total number of patient-months of observation for the group – 521.

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[4] Upper and lower quartiles.

No confirmed RSV infection cases in the analyzed sample of children were reported throughout the epidemic period[5]. In tote, 61 ARVI cases were registered in 35 children. No RSV-associated LRTI hospitalized were registered in the record forms. 7 hospitalizations were registered throughout the observation period: 3 hospitalizations were caused by aspiration pneumonia (in 1 child); the reason was not stated in 4 cases. No cases of admission to RICU or APV during hospitalization (any cause) were registered.

Undesirable phenomena (emesis, anxiety) were observed 3 times in 1 child (0.53%) 1 day after each palivizumab injection.

The estimated number of the RSV-associated hospitalizations in that population in the absence of immune prevention calculated in the model according to the literature data is given tb. 4.

Given the data on the rate of inpatient medical care rendering to the control groups at RICU in the RCT of palivizumab efficacy and safety [12, 13], we may presume that children would have required RICU care in 13 cases.

Given the weighted average rate of lethal outcomes during the severe RSV-associated LRTI hospitalization given in the trial [15], we may have expected 1 death in the group of children under study (tb. 5). As a result we may presume that use of palivizumab in the group of children under study allowed preserving 69 life years (according to the Federal State Statistics Service, estimated life expectancy at birth was 70.24 years of age [17] given that the death is prevented during the first year of life).

Table 4. Estimated number of the RSV infection hospitalizations in the absence of prevention with palivizumab.

Subgroup	RSV infection hospitalization risk	Number of observation patient-months	Estimated number of hospitalizations*	Corrected** number of hospitalizations
A. BPD				
A.1. Children of 0-<6 months of age	0.0938	134	13	24
A.2. Children of 6-<12 months of age	0.0357	91	3	6
A.3. Children of 12-24 months of age	0.0122	59	1	1
B. CHD				
B.1. Children of 0-<6 months of age	0.0201	146	3	6
B.2. Children of 6-<12 months of age	0.0106	16	0	0
B.3. Children of 12-24 months of age	0.003	4	0	0
C. Prematurity				
C.1. Children of 0-<6 months of age	0.0136	69	1	2
C.2. Children of	0.0066	2	0	0

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[5] RSV testing was not conducted in all ARVI cases.

6-<12 months of age				
C.3. Children of 12-24 months of age	0.0020	0	0	0
Total	-	521	21	39

Note. * - calculated according to the data of T.G. Boyce et al. [10] by multiplying the number of observation patient-months by the RSV-associated LRTI hospitalization risk with subsequent rounding to the nearest whole number; ** - according to the correction coefficient (1.89) for the higher hospitalization rate in the RF in comparison with the USA.
RSV – respiratory syncytial virus, BPD – bronchopulmonary dysplasia, CHD – congenital heart disease.

Table 5. Estimated number of lethal outcomes due to the RSV-associated LRTI in the observed group.

Groups	Estimated number of hospitalizations in the group	Weighted average rate of lethal outcomes at the severe RSV-associated LRTI hospitalization, in %*	Estimated number of lethal outcomes**
BPD	31	3.1	1
CHD	6	5.3	0
Prematurity	2	1.1	0
Total	39	-	1

Note. According to S.M. Szabo et al. [15]; ** - calculated by multiplying the estimated number of hospitalizations by the rate of lethal outcomes (in %) and rounded to the nearest whole number.
RSV – respiratory syncytial virus, LRTI – lower respiratory tract infections, BPD – bronchopulmonary dysplasia, CHD – congenital heart disease.

Expenses for the group under study and estimated expenses in the absence of immune prevention

RSV infection immune prevention program expenses equaled to 33,518,514.60 rubles, including 33,407,160.30 rubles of expenses for purchase of palivizumab and 111,354.26 rubles of expenses for the additional appointments for drug injections. It equals to 176,817.54 rubles per child involved in the trial, including 176,757.46 rubles of expenses for palivizumab and 60.08 rubles of expenses for appointments.

As there were no RSV infection-associated hospitalizations in the group under study, therefore, there were no expenses associated with them.

In the absence of immune prevention with palivizumab, expenses for inpatient treatment of the severe RSV-associated LRTI would equal to 1,698,103.90 rubles, including 1,520,136.29 rubles of expenses for hospitalization (per completed case) and 177,967.61 rubles of expenses for medical care rendering at RICU.

Thus, the difference between expenses for the children involved in the trial in the presence/absence of immune prevention equals to 31,820,410.68 rubles (or 168,361.96 rubles per child). Cost effectiveness increment in that case is 461,165.37 rubles per 1 disability-adjusted life year.

Economic damage (lost gross domestic product, GDP) in the event of death of 1 child using correction for employment and life expectancy within the economic activity period (from 15 to

72 years of age) would be equal to 29,760,927.36 rubles, i.e. it would be close to the revealed difference in expenses in the presence and absence of immune prevention program. Therefore, additional expenses for palivizumab injection are largely compensated by the averted economic damage due to the estimated infantile mortality decrease.

DISCUSSION
Our model trial showed that use of palivizumab in 189 children with high risk of severe RSV-associated LRTI has probably allowed preventing up to 39 hospitalizations, including 13 cases of care rendering at RICU and 1 death.

Neither the statistical review nor sampling trials neither in Moscow nor in the RF in general feature data on the RSV-associated LRTI hospitalization rate among premature children and children with HSCHD/BPD (the only available data regard the RSV infection share of hospitalizations in different groups of children). The publication dedicated to the RSV infection immunization program results for the previous epidemic season featured the number of hospitalizations before palivizumab injection among the children involved in the program, although the observation period was short (140 children were being observed for 3 months) [8]. That is why we calculated the number of prevented hospitalizations on the basis of a foreign trial – the only trial studying the frequency of inpatient treatment of the RSV-associated LRTI in a large group of children with different risk factors of severe course of the disease. Still, generally, palivizumab efficacy from the point of view of hospitalization rate is beyond any doubt, as has been mentioned before, and has been confirmed by trials of different design (RCT, cohort trials) and systematic reviews. In Moscow the program of RSV infection immune prevention with palivizumab for children of high risk categories has been being conducted for 2 epidemic seasons; no RSV-associated LRTI hospitalizations were registered in the groups of children taking palivizumab within these periods [8].

Immune prevention with palivizumab requires additional healthcare expenses, which cannot be compensated only by reduction in hospitalization expenses. Use of palivizumab in the analyzed group of children cost 33,518,514.60 rubles, whereas the estimated expenses for inpatient treatment of the RSV-associated LRTI would equal to 1,698,103.90 rubles.

However, the expenses for palivizumab are largely compensated, if we consider indirect expenses due to the child's mortality in the first years of life. The averted economic damage due to preservation of life of 1 child is 29,760,927.36 rubles, whereas the estimated expenses for the whole group of children involved in the analysis in the absence of immune prevention are almost equal to the expenses for use of palivizumab.

Cost effectiveness increment (added value of 1 year of life preserved owing to use of palivizumab) equaled to 461,165.37 rubles. It is known that there is no unified approach to interpretation of this parameter in Russia. The World Health Organization recommended using triple GDP per capita in money terms as the cost effectiveness threshold of application of medical technologies in the form of expenses increment per 1 life year with correction for disability (disability-adjusted life year) [21], which may be considered an equivalent of expenses per year of quality life at a stretch (quality-adjusted life-year, QALY). It is impossible to objectively assess the number of quality-adjusted life-years in the RF due to the lack of representative data on life quality in various health conditions in the Russian population. The number of quality life years is not a common indicator of evaluation of medical technologies application results in Russia (unlike Great Britain). We believe that in this situation it is possible to use the number of disability-adjusted life years instead of the number of quality-adjusted life-years in order to interpret economic assessment results. Cost effectiveness increment (cost of 1 disability-adjusted life year) for palivizumab only slightly exceeds the GDP per capita and is considerably lower than the triple GDP per capita[6] in comparison with the absence of specific immune prevention; this allows considering its use substantiated and reasonable.

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[6] Population of Russia in 2012 – 143 mn people, GDP in 2012 – 62,559.1 bn rubles, GDP per capita – 437,476.22 rubles: thus, the triple GDP per capita threshold is 1,312,428.67 rubles.

We calculated the number of prevented deaths, disability-adjusted life years and prevented hospitalizations on the basis of foreign data – results of a systematic review of 34 trials [15]. It ought to be noted that, as we have mentioned before, the data on hospital mortality of children with RSV infection generally are extremely limited, whereas the available data vary greatly. There have been Russian data neither on the severe RSV-associated LRTI mortality rate among premature children, children with BPD and CHD nor on hospitalizations. However, the results we obtained do not contradict the objective data on causes of death in children of the first year of life. It is known that respiratory tract diseases have for many years been among causes of death in children of the first year of life: thus, according to the Federal State Statistics Service, 10 children died of such diseases in 2010[7], 20 – in 2011, 12 – in 2012, although there are no available data on their characteristic features [22].

Other researchers also mention variability of data on severe RSV-associated LRTI mortality. Without any doubt, this affects palivizumab economic assessment results. Thus, a systematic review of palivizumab economic research revealed the fluctuations of cost effectiveness increment from £25,800 to 404,900 per 1 disability-adjusted life year[8]; the discrepancy is caused by the use of different RSV infection mortality parameters [23].

According to most foreign trials, the key factor determining reasonability of use of palivizumab in the conditions of limited resources is an accurate selection of children subject to immune prevention: it ought to involve children with the highest risk of severe course and death of RSV infection. Thus, according to the British palivizumab economic research review, cost effectiveness increment was lower than the threshold willingness to pay (£30,000/QALY) only in the subgroups of children with the highest risk of severe LRTI [24]. Similar data were observed in other economic research reviews as well: the higher the risk of severe LRTI development in the children involved in the analysis, the more convincing the palivizumab cost effectiveness [25]. Risk factors and their combinations, the presence of which determine cost effectiveness of RS infection immune prevention with palivizumab, also vary slightly from trial to trial, though most works distinguish gestation age (less than 35 weeks), BPD and hemodynamically significant CHD.

Thus, a British trial featured the following cost effectiveness increment values: $41,658[9]/QALY for children born on or before the 35th gestation week; $58,648/QALY for children with BPD; $18,653/QALY for children with CHD. The similar results were obtained by Australian researchers: $30,114/QALY, $46,351/QALY, $16,566/QALY, respectively. The Dutch trial yielded the following values: $26,862/QALY for premature children, $33,962/QALY for children with BPD and $10,279/QALY for children with CHD. One of the lowest cost effectiveness increment values for children with BPD was obtained by an Italian trial - $4,331/QALY [25].

The only constraint of our trial was lack of the control group and use of foreign data sources to model RSV infection outcomes in the absence of immune prevention. A full-scale clinical economic trial aimed at gathering real data both on the group taking palivizumab and on the control group will allow obtaining more accurate estimates of palivizumab cost effectiveness for RSV infection prevention.

CONCLUSIONS
1. No RSV infection hospitalizations were registered in the sample of 189 children of the first year of life with risk factors of severe course of the RSV-associated LRTI who had received 3-5 palivizumab injections for RSV infection immune prevention in the season

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[7] Endogenous causes of death (due to mother's health status and intrauterine effect on the forming fetus, including congenital pneumonia) are listed separately.
[8] The obtained cost effectiveness values were converted into pounds sterling (price of 2006) for comparison purposes.
[9] The values are given in Canadian dollars for comparison purposes; quoted according to the text of systematic review [22].

of 2012/2013. Given the data on hospitalization rate in similar groups of children obtained in the earlier trials, we could have expected 39 hospitalizations, including 13 cases of medical care rendering at RICU and 1 lethal outcome, in the analyzed group in the absence of immune prevention.

2. Cost effectiveness increment in the event of use of palivizumab is 461,165.37 rubles per 1 disability-adjusted life year, which is lower than the triple GDP per capita, which is why immune prevention of RSV infection among children with high risk of severe course of this pathology may be considered economically sound.

3. The averted economic damage (lost GDP) in the event of death of 1 child is 29.8 mn rubles; this largely compensates additional expenses for the program of immune prevention with palivizumab in the sample under analysis (31.8 mn rubles).

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