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Immune prevention of respiratory-syncytial virus infection: 15 years of world experience

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The article is dedicated to one of the most important issues of modern neonatology – prevention of respiratory-syncytial virus infection, which is a frequent cause of bronchiolites and pneumoniae in infants and neonates, especially premature infants. The latter belong to the high-risk group for the development of this infection with unfavorable outcome. The authors present detailed data on epidemiology and world spread of respiratory-syncytial virus infection, its consequences (short-term and long-term) and prevention possibilities. The authors demonstrate efficacy of passive palivizumab (humanized monoclonal antibody) immune prevention on the basis of multiple studies conducted in different countries. The authors show the process of formation of national recommendations for immune prevention of development of this infection. Apart from the main risk groups for the development of respiratory-syncytial virus infection, acknowledged by the scientists, the authors also present additional groups – children with mucoviscidosis, Down's syndrome, neuromuscular diseases and immune compromised patients due to the primary immune deficiency or in the setting of immune suppressive therapy.

Keywords: *respiratory-syncytial virus infection, epidemiology, morbidity, consequences, risk groups, prevention, palivizumab, efficacy, safety, children, neonates, premature infants.*

A symposium dedicated to the 15-years-long world experience of palivizumab application for immune prevention of respiratory-syncytial virus infection in the framework of the XI World Congress of Perinatal Medicine (19-22 June 2013, Moscow). Leading specialists in neonatology took part in the symposium; their reports touched upon the current state of RSV-infection issue in infants and the approaches made in different countries to resolve it.

The President of the World Association of Perinatal Medicine Xavier Carbonell-Estrany summed up the accumulated world data on RSV-infection severity, efficacy of immune prevention of the infection and additional complicating factors in his report “RSV-infection: epidemiology, disease burden, risk factors and efficacy of preventive measures”. The Chairman of the Neonatal Infections Department of the Italian Association of Neonatology and advisor of the European Medicines Agency Paolo Manzoni analyzed experience of developing recommendations and introducing RSV-infection immune prevention programs in the European Union in his report “Different approaches – the common goal: European experience of RSV-infection immune prevention”. Professor of neonatology Satoshi Ibara from Japan – one of the leading countries of immune prevention coverage of the risk group children – showed ways of improving the immunization program in his report “Extending the frontiers: New risk groups for introduction to the RSV-infection prevention program”. In the end, Professor Elena Keshishyan told about the activity of accumulation of experience in the risk group children's immunization in Russia in her report “RSV-infection immune prevention in Russia: Experience of application and the first results”.

This review presents data on the accumulated clinical experience of palivizumab application in the last 15 years and practical results of introduction of the RSV-infection immune prevention programs in the world.

RSV-infection – serious risk for infants

Respiratory-syncytial virus infection (RSVI) takes a prominent position among causative agents of acute respiratory infections. RSVI-caused morbidity is characteristic of all human life periods; however, the most RSVI susceptible group is infants; in them, the infection may affect lower respiratory tract. At present, RS-virus is considered the most frequent causes of lower respiratory tract infections (LRTI) – bronchiolites and pneumoniae – in neonates and infants. RSVI often results in hospitalization and even in lethal outcome in this group. According to the results of a meta-analysis of the world literature data, 33.8 mn LRTI cases were observed in children under 5 years of age in 2005 [95% confidence interval (CI) – 19.3-46.2]; at least 3.4 (2.8-4.3) mn children were hospitalized for this reason, 66,000-199,000 died of it [1]. In older children, RSV causes a relatively mild respiratory tract's affection, manifesting itself with nasopharyngitis and bronchitis, including exacerbation of chronic bronchitis or pneumonia. Primary RSV-infection often develops in children of 6 weeks – 2 years of age [2]. By 2 years of age, almost all children have at least once contracted RSV; half of them develop this infection twice [3].

Epidemiology and spread of RSV-infection

RSV is spread in almost all climatic zones and causes seasonal infection outbreaks, usually in the autumn-winter period in regions with change of seasons or in the raining season in countries with tropical climate [4]. However, timeframe of the infection's epidemic season may vary on the basis of the local climatic and demographic peculiarities even within one geographic zone or country. Identification of the infection spread algorithm characteristic of one or another territory is an important morbidity control factor. Thus, long-term European observations allowed determining that epidemiologic data are generally comparable in all the territories of the European Union; infection outbreaks take place in winter; first they affect the Baltic Sea regions, then the epidemic spreads from North to South and West [4].

Annual RSV monitoring activity allows determining boundaries of the infection's epidemic season and the time of the epidemic season's beginning. These systems are established in the USA and several European countries. The monitoring is based on the identification of etiology of ARVI resulting in hospitalization to the so called symptom clinics. This allows tracking morbidity rate and determining the threshold of the epidemic season's beginning. E.g., such a threshold in the USA is 10% of antigen-confirmed hospitalizations for RSV-bronchiolites [5]. The system of RSVI epidemiologic surveillance has been in operation in Italy since 1998; it is based on 2 large-scale trials. The RADAR trial was conducted to obtain data on RSVI spread in Italy in infants hospitalized for lower respiratory tract infection. It appeared that morbidity rate of the hospitalization-requiring RSVI increases fivefold from November to February – the epidemiologic season's peak [6]. Another trial – Osservatorio RSV Study – is a large-scale monitoring program providing uninterrupted epidemiologic surveillance since 2001. All the obtained information is available to doctors online on a specialized web-site. These data allow drawing a monthly RSVI morbidity dynamics graph for 3 geographic zones of Italy – “North”, “Center” and “South” – and maintaining individual preventive regimen [7].

Severe RSV-associated ARVI course in small children is typical of “autumn-spring” season; they constitute up to 35% of all hospitalizations. In Russia, RSVI morbidity was for the first time studied in the epidemiologic season 2008-2009. 519 children under 2 years of age hospitalized with lower respiratory tract infections were examined at 11 clinical centers in the RF from 11 September 2008 to 26 April 2009. RSV was revealed in 197 cases (38%; 95% CI – 33.8-42.3). Infectious season began in November; the peak was registered in March-April, when 62% of the hospitalized children appeared RSV-positive [8, 9].

According to the symptomatic surveillance data obtained at the premises of inpatient hospitals in 9 cities of Russia in epidemiologic season 2012-2013, ARVI infection cases in children under 2 years of age requiring hospitalization were caused by RSV-infection in 30% of cases: in children under 1 year of age – in 34.9% of cases, in children of 1-2 years of age – in 21.4% of cases [10]. These epidemiologic data reconfirm results of the trial conducted in 2009.

Short-term RSV-infection effects: morbidity and mortality

RSV is a considerable burden for public health as a primary LRTI development factor due to the high rate of hospitalization and mortality among the risk group children. A considerable number of children developing RSVI and dying of it live in the developing countries; however, the infection poses a serious issue for the developed countries as well. Thus, the hospitalization-requiring RSV-infection morbidity rate in infants in the USA in 1997-2006 was 26.9 per 1,000 and was maximal in children of 0-3 months of age (48.9 per 1,000) [11]. The rate of visits to doctors and emergency care units and hospitalizations is several times higher at RSVI than at influenza in children of 0-23 months of age [12]. W. Thompson et al. analyzed mortality data of the US National Center for Health Statistics (NCHS) to estimate annual influenza and RSVI mortality. Influenza- and RSV-caused lethal outcomes were estimated simultaneously for seasons 1990/91-1998/99. It appeared that RSV is the main viral cause of fatal outcomes in infants; it exceeds influenza mortality rate 8.8 times (mortality rates 5.3 and 0.6 per 100,000 patient-years, respectively) [13].

RSV-infection morbidity and mortality risk is especially high in children with the established risk factors of its severe course: children born before the 36th gestation week, with hemodynamically significant congenital heart disease (CHD) or bronchopulmonary dysplasia (BPD). Risk of RSV-bronchiolitis development with severe respiratory failure phenomena requiring massive infusion and inhalation therapy and even artificial lung ventilation (ALV) [14] is the highest in these children. According to different data, RSVI mortality in children with BPD and CHD is 2-37%; in children born before the 36th gestation week – 0-6.1% [15]; the variation is caused by the level of economy and public health development in the country. According to the analysis of 36 epidemiologic trials, RSVI mortality in the developing countries reaches 5.3-6.2%, in the developed countries – 0.3-0.5% [4]. As has already been mentioned, risk factors play an important role in this process. RSV-bronchiolitis mortality among the initially healthy term infants reaches 1.3 per 100,000. In premature infants of low body weight (less than 1,500 g) it is 23 times higher; in children born before the 32nd gestation week – 15 times higher [16].

Possibility of RSV-infection immune prevention

Possibilities of RSV-infection treatment are limited, which is why prevention comes to the fore. First vaccine for RSVI treatment – formalin-inactivated virus – was applied in the 1960s and resulted in the dramatic increase in the disease severity and mortality among the vaccinated children, as RSV antigens induce non-balanced immune response with shift to the hyperactive inflammatory process in the respiratory tract (excessive pulmonary infiltration of T lymphocytes, local eosinophilia, neutrophilia, monocytophilia) and bronchial obstruction [17]. The research resumed; however, there still are no licensed RSVI vaccines. Insufficient knowledge of RSVI pathogenesis mechanisms results in impossibility of complete elimination of risk of immunopathology-induced postvaccinal complications. Vaccines under development and in different stages of clinical trials may be effective; however, their large-scale implementation is hardly probable.

Passive immunization methods were developed to reduce RSVI course severity. First, it was achieved by intravenous immunoglobulins (IVIG). This practice allowed decreasing the disease course severity and duration of an infected child's inpatient stay. The IVIG were further improved by means of enrichment with RSV-neutralizing antibodies. The PREVENT trial revealed that the disease duration, amount of hospitalizations, need in oxygen support and the respiratory tract's pathology severity decreased in children under 2 years of age with

bronchopulmonary dysplasia and in children born in or before the 35th gestation week when RSV-IG are applied [18]. This allowed the US Food and Drug Administration (FDA) approving an RSV-IG-based drug for RSVI prevention in these groups of children in 1996.

Application of RSV-IG had a range of restrictions. First of all, the drug's administration required an hours-long intravenous infusion complicated in small children with poor venous access and resulting in hypervolemia. Second of all, manufacture of the drug of human blood did not completely eliminated infection risk. Third of all, antibodies could interfere with activity of live virus vaccines. A special trial showed that RSV-IG application does not reduce amount of hospitalization for the RSV-induced respiratory tract's pathology among children with congenital heart disease or cardiomyopathy. Moreover, fatal outcomes became more frequent in the operated children. Prohibition of RSV-IG application in children with congenital heart disease and the aforementioned restrictions promoted the further search for an effective immune prevention method, which resulted in the development of palivizumab.

Palivizumab is humanized monoclonal antibodies connecting with F-protein of RSV. *In vitro* palivizumab has a 50-100 times higher affinity to RSV than RSV-IG, which is why immunoglobulin-based drugs have lost applicability since its introduction. Injection volume of palivizumab is 100 times smaller than of its predecessors. In June 1998, palivizumab was approved by the FDA for the severe RSV-induced lower respiratory tract pathology prevention in premature infants and children with bronchopulmonary dysplasia. Recommendations of the American Academy of Pediatrics (AAP) – basis for the formulation of other national recommendations – were published in the same year. One year later palivizumab was approved in Europe and Japan started palivizumab trials, on the basis of which it was approved in this country in 2002. In 2003, palivizumab was approved in Europe and the USA for application in children with hemodynamically significant congenital heart disease. Revisions of AAP recommendations allowing for the data of the recent pharmacoeconomic and epidemiologic trials were issued in 2006 and 2009. In 2010 palivizumab was approved in Russia. It ought to be noted that palivizumab ensures passive immune prevention of RSVI – a fundamental difference from a vaccine. Vaccination is essentially the administration of an antigen for antibody production stimulation. Unlike active immunization, passive immunization is conducted by administering ready antibodies and is aimed at quick compensation of the body's immunological exposure by means of an effective, though short-term, immune response. Thus, passive immunization does not burden immature immune system of premature infants with additional stress; this is one of the reasons of high safety of this approach.

Palivizumab in clinical practice: efficacy and safety

Evidentiary foundation of palivizumab efficacy and safety is based on the international randomized double-blind placebo-controlled trial Impact-RSV; its results were published in 1998. It involved children born in or before the 35th gestation week under 6 months of age and children under 2 years of age with bronchopulmonary dysplasia requiring constant medical care. Hemodynamically significant heart disease served as an exclusion factor. A drug of 15 mg/kg of body weight or placebo was administered to each child monthly. As a result, amount of hospitalizations for RSVI in the group of children receiving palivizumab decreased by 55%. This parameter in the placebo group was 10.6%, in the palivizumab group – 4.8% ($p<0.001$). Significant decrease in the amount of hospitalizations for RSVI at immune prevention was observed in premature infants both with BPD (by 39%; $p=0.038$) and without it (by 78%; $p<0.001$) as well. Significant decrease in the RSVI hospitalization duration (62.6 days in the placebo group; 36.4 days in the palivizumab group; $p<0.001$), total hospitalization duration with need in additional oxygen (50.6 and 30.3 days; $p<0.001$), total intensive care unit RSV-hospitalization duration (47.4 and 29.6 days; $p<0.001$) and rate of admission to the intensive care unit (3% of patients in the placebo group; 1.3% in the palivizumab group; $p=0.026$) was registered in the group of patients receiving palivizumab. No significant differences were observed between placebo and palivizumab in terms of amount of undesirable phenomena.

Injection site reaction were very rare (1.8% - placebo; 2.7% - palivizumab). Injection site was most often characterized by temporary moderate reddening [19].

The subsequent international double-blind placebo-controlled trial conducted by Feltes et al. evaluated efficacy and safety in children under 2 years of age with hemodynamically significant congenital heart disease, which had not been completely corrected surgically. The worst patients, including patients requiring artificial ventilation, heart transplantation candidates and several other groups of patients were excluded. The trial revealed that palivizumab prevention results in the RSV-infection hospitalization rate reduction in children by 45% ($p=0.003$). This parameter was 9.7% in the placebo group, 5.3% - in the palivizumab group. Moreover, the children randomized to the palivizumab group had shorter RSVI hospitalization duration (129 days in the placebo group per 100 children; 57.4 days in the palivizumab group; $p=0.003$) and shorter RSVI hospitalization additional oxygen support duration (101.5 days and 27.9 days per 100 children; $p=0.014$). Rate of undesirable phenomena was similar in both groups [20].

Since then, palivizumab efficacy and safety have been confirmed numerous times by data of the so called registers that are usually formed in the framework of large-scale observation trials. Table 1 gives information on the large-scale registers that have been developed since palivizumab was approved in 1998. Trial by C. Pedraz et al. may be used to exemplify the register-confirmed palivizumab efficacy – a prospective multicenter cohort trial with historical control conducted in Spain in the course of 4 consecutive RSVI seasons. The group under study involved premature infants born before the 32nd gestation week under 6 months of age with/without BPD. Historical control was essentially a cohort of 1,583 premature infants observed in the course of seasons 1998/99 and 1999/2000 at 14 and 26 Spanish clinical centers, respectively, who were not receiving palivizumab. The immunization group involved 1,919 premature infants, who had been receiving palivizumab in the course of seasons 2000/01 and 2001/02 at 27 and 21 clinical centers after the drug was approved in Spain. RSVI hospitalization rate in the group of children, who were not receiving palivizumab, was 13.25%, while this parameter in the immunization group was 3.95%. Thus, the trial revealed a 70% RSVI hospitalization rate reduction in premature infants in case of palivizumab immunization. Premature infants not receiving palivizumab are subject to higher risk of RSV-infection hospitalization in comparison with children receiving immune prevention [odds ratio (OR) – 3.85; 95% CI – 2.83-5.25]. Significant difference in the RSV-hospitalization rate between cohorts remained at the analysis of subgroups as well: among children <28 GA weeks – 58.4%, of 29-32 GA weeks – 74.7%, among children with BPD – 72% [21].

Table 1. Registers developed since palivizumab approval in 1998.

Parameters	CARESS	Oh et al.	Romero et al.	Frogel et al.	Pedraz et al.	Lacaze-Masmonteil et al.	Simon et al.
Country	Canada	Canada	USA	USA	Spain	France	Germany
Years	2005-2011	1999-2000	1998-2000	2000-2004	2000-2002	1999-2000	2002-2007
Population	All children receiving palivizumab	Children involved in the special evaluation program	All children receiving palivizumab	All children receiving palivizumab	All children receiving palivizumab (retrospective analysis)	Children involved in the special evaluation program	All children receiving palivizumab
Patients (n)	10,452	444	1,839 (1998-1999) 2,830 (1999-2000)	19,548	1,919	547	10,686
Share of RSVI hospitalizations*, %	1.6	2.4	2.3-2.4	1.3	3.95	8.10	2.5

Note. RSVI – respiratory-syncytial virus infection.

* - share of hospitalizations in the risk group children not receiving palivizumab varies from 9 to 14% (according to different trials) [18-20].

An important advantage of registers is the possibility of determining additional factors increasing risk and severity of RSV-infection course. Thus, risk of RSVI hospitalization in both Spanish cohorts reduced in direct proportion to the gestation age increase (OR – 0.86; 95% CI – 0.77-0.96; $p=0.006$), age of >3 months by the RSVI season (OR – 0.55; 95% CI – 0.33-0.92; $p=0.02$) and parents with completed basic education (OR – 0.47; 95% CI – 0.24-0.93; $p=0.02$). On the other hand, existence of school-age brothers and sisters determined the trend of RSVI hospitalization risk increase (OR – 1.6; 95% CI – 0.99-2.69; $p=0.05$) [21].

Meta-analysis of 10 randomized controlled and cohort trials of the drug conducted by the research team of P. Checchia, which involved ca. 15,000 children of severe RSV-infection course risk groups in total, was a certain intermediate total of palivizumab efficacy research. The attained results indicate reduction in the total mortality and antigen-confirmed RSV hospitalization rate in children, who had received passive immunization. Thus, total mortality rate decreased 4.3 times in premature infants with gestation age of less than 32 weeks. RSV-infection hospitalization rate in the immunized premature infants of that group was 2.9 times lower than in the control group children, who had not received immunization [22].

Delayed RSV-infection effects and possibility of their correction at immunization

Apart from the main RSVI effects associated with hospitalization and potential mortality of the risk group children, there are also delayed effects. The children, who had undergone RSV-associated LRTI, in the future require medical care to a larger extent than their peers without such an anamnesis. A study of healthcare utilization and mortality in premature infants discharged from inpatient hospital after RSVI and in their peers, who had not had RSV-infection, was conducted in Canada. The former visited doctors and were hospitalized more often and had a 20 times higher sudden death risk than the premature infants, who had not had RSV-infection (6.1 and 0.3%; $p<0.001$) [23].

RSV-associated bronchiolitis undergone in infancy is often accompanied by development of symptoms of bronchial obstruction and asthma, which may persist for several years. A prospective study compared children of 7.5 years of age: 47 children hospitalized for RSV-bronchiolitis in early childhood and a control group of 93 children. It appeared that the rate of bronchial obstruction and asthma development was significantly higher in the children who had had RSV-bronchiolitis than in the control group children. Moreover, higher rate of clinical allergy to the inhaled allergens (indicated by a higher level of allergic rhinoconjunctivitis) was revealed in the RSV-bronchiolitis group children in comparison with the control group ($p=0.007$) [24]. Thus, the RSV-induced severe bronchiolitis, which had developed in early childhood, is a high risk factor of allergic asthma development in early puberty. The number of children suffering from such conditions as reactive respiratory tract diseases and asthma may probably be reduced by RSBI prevention.

As far as children, who had had RSV-associated LRTI in the early childhood, later have problems with breathing, including appearance of sibilant rales, it was assumed that palivizumab RSVI prevention may not only reduce the hospitalization rate of the risk group children, but also promote the respiratory function's improvement in such patients. A cohort of premature infants without chronic pulmonary diseases born before the 35th gestation week was studied in order to confirm this hypothesis. The first group involved 191 children receiving palivizumab during the epidemic season and not hospitalized for RSVI, the second – 230 unimmunized children, 76 out of whom were hospitalized for RSVI. The children were observed for sibilant rales for 24 months, starting from the age of 19 months (on the average). The rate of sibilant rales, including the rales diagnosed by doctors, was considerably lower in the group of children receiving palivizumab (13 and 8%, respectively) in comparison with both a group of patients without prevention (26%; $p=0.001$ and 16%; $p=0.011$, respectively) and a subgroup of children who had not been receiving prevention and not hospitalized for RSVI (23%; $p=0.022$ and 16%; $p=0.027$, respectively) [25].

Data of a double-blind placebo-controlled trial with 429 children born in the 33rd-35th gestation week randomized into 2 groups were published in May 2013. The first group received palivizumab during the RSVI epidemic season, the second (n=215) – placebo. The trial estimated the number of days when sibilant rales were observed in children. Palivizumab application allowed reducing the total number of days with observed sibilant rales in infants by 61% (95% CI – 56-65): 930 out of 53,075 days (1.8%) in the immune prevention group in comparison with 2,309 out of 51,726 days (4.5%) in the placebo group. Thus, RSVI immune prevention course during the epidemic season results in the significant and prolong improvement of respiratory state in infants [26].

Approaches to immune prevention of RSV-infection in the world

As RSV-bronchiolitis and pneumonia may be life-threatening for some children, many countries formulated national standards of the severe RSV-infection prevention in the revealed risk groups and started financing special preventive programs. Efficient specific immunization of the risk group children may considerably decrease the rate of severe forms of the infection, hospitalization and mortality [9, 19-22]. At the same time, the need in financing RSVI immune prevention programs in a large group of premature infants results in the generation of differentiated approaches to the severe infection risk estimation. There exist different approaches to the RSVI immune prevention in premature infants in the world. As has been mentioned before, epidemiologic situation may vary in different countries. Possibilities of financial immune prevention provision also differ, especially given the need of groups of the most severely ill children in immune prevention. The leading countries with experience of palivizumab application have formulated their national recommendations on the basis of the available international and local trials.

However, all these approaches have one thing in common: medical community unequivocally recommends RSVI immune prevention in the children that are most susceptible to the infection; the state is to provide financing of these programs. Such a group of extremely susceptible infants involved premature infants born before the 32nd (33rd) gestation week and children with BPD and hemodynamically significant CHD. Preventive measures in the small premature infants born before or in the 28th gestation week may be conducted until 1 year of age, in children of 29-32 weeks of gestation age – until 6 months of age, in children with BPD and CHD – until the age of 2 years (tb. 2). Epidemic season for the immunization is usually determined on the basis of the local epidemic data, takes place in autumn/winter/spring and embraces 5 months (in Europe and the USA it is usually November-March). However, the immune prevention duration may be prolonged in several countries, e.g. in Japan, where on this stage the immunization at most clinics starts in September and ends in March-April [27].

As for the involvement of children born in the 33rd-35th gestation week (the most numerous in the group of premature infants) in the immune prevention program, the algorithms for evaluation and account of additional risk factors of severe RSVI course are developed and applied.



For instance, 2 large-scale trials were conducted in Spain in the framework of developing a national algorithm; they were aimed at revealing factors predisposing to the severer infection course. 186 children hospitalized for RSVI and 371 control group children were examined in the framework of the trial FLIP-1. 20.5% of children required intensive therapy. Statistical analysis revealed that the key risk factors are absolute age by the season beginning, shorter than 2 months breast feeding duration, existence of school-age siblings or 4 and more relatives sharing the same residence and sibilant rales in family anamnesis [28]. These factors and also additional factors were verified in the framework of the trial FLIP-2, which involved 202 children hospitalized for RSV and 5,239 control group children. It was revealed that the main risk factors in children born in the 32nd-35th gestation weeks are birth 10 weeks before or after the RSVI season and existence of school-age siblings. The secondary risk factors were male sex and smoking during pregnancy. Comparative analysis of different combinations of risk factors allowed concluding that the RSVI

hospitalization risk is 3.3 times higher in children born in the 32nd-35th gestation week with 2 or more risk factors, which is why they require immune prevention [29].

A large number of risk factors increasing infection risk and aggravating RSVI severity course have been revealed; research in the field continues. The range of factors confirmed by 3 large-scale trials and employed by international recommendations for RSVI severe course risk evaluation is given in tb. 3.

Table 2.

Table 2. Review of international recommendations on the prevention of PCBS infection, 2012

Children	 France (11/2008)	 Germany (09/2008)	 Italy	 Spain	 Great Britain	 Canada	 Japan	 USA
≤28 GA weeks	<12 months	≤12 months	<12 months	<12 months	none	≤6 months	<12 months	≤6 months
29–32 GA weeks	From 29 ⁺ to 31 ⁺ GA weeks <6 months by the season beginning	≤6 months 2/3 RF	<12 months	<6 months	none	≤6 months	<6 months	≤6 months
33–35 GA weeks	None	≤6 months + 2/3 (risk factor)	<12 months + 2 (risk factor)	<6 months + 2/7 (risk factor)	none	≤6 months	<6 months	<3 months
CHD	<24 months	≤24 months	≤24 months	<24 months	<24 months	≤24 months	<24 months	<24 months
BPD/CPD	<24 months, Requiring medical support in the latest 6 months	≤24 months Or in the 1 st -28 th day of life	<24 months	<24 months	<24 months	≤24 months	<24 months	<24 months
Other	<6 months: – with mucoviscidosis; – other pulmonary or neuromuscular pathology; – immunodeficiency	-	-	-	Immunodeficiency	Immunodeficiency Mucoviscidosis	-	Congenital respiratory tract anomalies Neuromuscular pathology

Note. GA – gestation age, CHD – congenital heart disease, BPD – bronchopulmonary dysplasia, CPD – chronic pulmonary disease.

Table 3.

Table 3. Risk factors of severe PCBS infection course listed in the international recommendations

Risk factors	USA	Spain	Canada
Age <6 months by the beginning of the RSV season	X	X	X
Siblings (preschool or school age)	X	X	X
Attendance at day children's institutions	X		X
Level of pollution			X
Accommodation at a populous building/apartment (≥4, >5)		X	X
Congenital disorders	X		
Severe neuromuscular pathology	X		
Breast feeding ≤2 months		X	
Sibillant rates in family anamnesis		X	
Intrauterine fetal hypertrophy			X
Masculine gender			X

In general, variety of approaches to immunization of children born in the 32nd-35th gestation week applied in different countries is given in pic. 1. Analysis of epidemiologic, demographic, clinical, organizational and financial variables in a given country or its region results in

formulation of a unique instrument of risk evaluation in each premature infant. Thus, palivizumab is now prescribed to all premature infants (born before the 36th gestation week) in 64.8% of national clinics in Japan (one of the leading countries in terms of immune prevention coverage of the risk group children), while the share of such hospitals in the first immunization season was only 24.5% [27].

Additional risk groups of severe course of RSV-infection

The current recommendations on RSVI prevention often touch upon only several groups of high risk of its severe course. The trial by Hall et al. estimated connection of RSVI severity course and immune system's condition in 608 RSVI-hospitalized children under 5 years of age. Children appeared to be immunocompromised due to chemotherapy, treatment with steroids or primary immunodeficiency in 47 cases. Infection took a severer course in such children regardless of age and resulted in death more often. It was also observed that the infection was of hospital-acquired nature in half of cases. The authors concluded that children with immune system's disorders of different genesis ought to be considered for RSVI prevention [30]. There are published data that palivizumab application in term infants with immunodeficiency of different genesis allows preventing RSVI development within the first 2 years of life. Lack of side effects is an additional argument pro immune prevention in these groups [31]. Up to 49% of research teams dealing with organ transplantation applied palivizumab in the first 2 years of children's life even in the absence of official recommendations [32].

Although the RSVI rate in patients with mucoviscidosis is the same as in the control population, these children require longer hospitalization and suffer from pulmonary function's disorders within several months after a lower respiratory tract infection [33]. Data on palivizumab efficacy in the setting of mucoviscidosis are contradictory. Retrospective analysis of one of the trials revealed tendencies to reduction in hospitalization rate and RSV detection at an acute respiratory infection, although the results did not reach the status of statistical significance due to the small sample size [34]. Russian researchers also detect the effectiveness of palivizumab in children with cystic fibrosis [35].

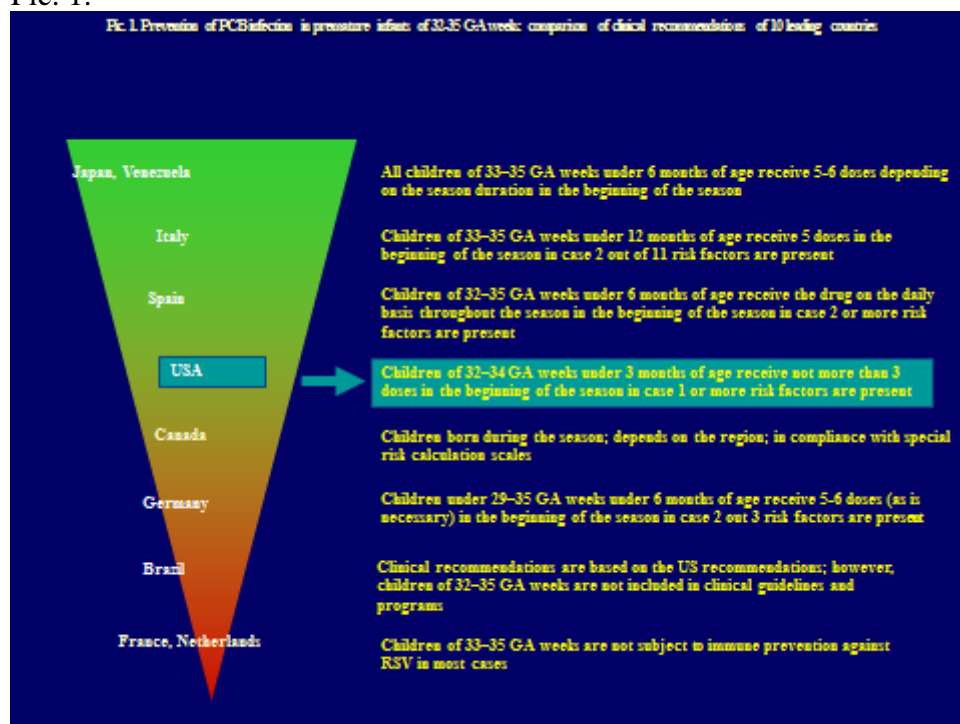
Another high risk group is children with Down's syndrome or children with neuromuscular diseases, who require intensive therapy and artificial ventilation and die more often [36, 37]. There has been no systemic study of palivizumab efficacy in these children; moreover, according to the preliminary data, need in intensive therapy, ALV and mortality did not decrease in the setting of palivizumab treatment in comparison with the control group. Real evaluation of passive immune prevention efficacy requires trials similar to Impact-RSV; according to experts, palivizumab application at present is reasonable in infants encountering problems with secretion evacuation due to the disease [38].

Thus, a potential range of preventive palivizumab application is rather large. Many of the mentioned "additional" diseases are not spread enough to become an object of research of randomized controlled trials. However, it ought not to become a hindrance in rendering care to the children in need. Possibility of palivizumab application is usually separately stipulated in cases not covered by recommendations based on the maximal level of evidence at formulation of guidelines based on the data of European registers.

According to the contemporary ideas and recommendations of the leading experts, particularly of Prof. Manzoni, Chairman and coordinator of the Neonatal Infections Department of the Italian Association of Neonatology and outside consultant of the EMEA (European Medicines Agency), the process of formulation of national recommendations on RSVI immune prevention is divided into a few stages. The first stage involves accumulation of local epidemiologic data. In the second stage it is required to evaluate the most characteristic risk factors for a given country or territory. In the third stage it is reasonable to apply the current AAP recommendations with allowances made for the previously established local peculiarities. In the fourth stage the formulated recommendations are to be endorsed by the experts in neonatology and then published. The recommendations may later be revised and corrected as new data are attained.

An active study of local RSVI morbidity specific features is going on in Russia: local epidemiologic data and the experience of immunization of the risk group children are accumulated; pharmacoeconomic efficacy of the prevention has preliminary been evaluated [8, 39-43]. Resolution of a difficult issue – preservation of children’s health, especially of the aforementioned risk group children – requires complex approaches and solutions synchronized on different levels of medical care rendering. Competent and consistent delivery of information both on the measures of everyday prevention and possibilities of drug protection against RSV remains a key aspect of work. International practice shows that these issues may be resolved by applying systematic approach accounting experience of other countries, local practice, interaction and control of the leading institutions participating in this process.

Pic. 1.



Note. GA – gestation age.

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