



Retrospective Analysis of Quality of Pharmacotherapy for Children with Acute Respiratory Infections on Background of ABC /VEN/ Frequency Analysis Based on Data of Patients' Medical Histories

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Abstract

Increase in frequency of acute respiratory viral infection (ARVI) and difficult economic situation in Ukraine require rational use of financial resources to treat this disease in children. Comprehensive analysis on background of additional pharmacoeconomic methods: ABC-, VEN- and frequency analysis based on study of results of 180 children with ARVI - allows to estimate cost of drugs in hospital of Burin town, Sumy region, Ukraine. It has been found out that part of money turned out to have been used inefficiently for treatment of children with ARVI and pharmacotherapy not always to be in line with government regulations because 16.15 % - 38.69 % of all funds were spent on drugs not included in Clinical Protocols for ARVI and related diseases. That is why there is an opportunity to cut down expenditures spent on unnecessary drugs during treatment period.

Keywords: *Drugs for treatment of children with acute respiratory viral infections, Clinical and economic analysis.*

Introduction

According to WHO about 90% of the world's population suffer from acute Respiratory Virus Infections (ARVI) annually. This is the most common disease not only on list of infectious diseases, but also in the system of overall morbidity. From 7 to 14 million [1] - 60-70% of them are children - suffer from ARVI including influenza in Ukraine annually. It happens due to peculiarities of immune system in children [2]. Around 40% of children with ARVI have complications: catarrh of upper respiratory tract, constrictive laryngitis, bronchitis, pneumonia.

Late start of pneumonia treatment leads to infant mortality. Infant mortality from pneumonia is 13.1 out of 10 thousand children [3] on average in Ukraine and pneumonia in the world is the reason 20% of infant mortality [4]. According to International Disease Classification of 10-th Revision ARVI refers to acute respiratory infections (ARI) and ARVI is a generalized

name for any respiratory viral infection. Today a significant number of known pathogens belong to 9 different groups of viruses: influenza, parainfluenza, adeno-, RS- (respiratory syncytial) pikorna-, korona-, reo-, entero-, ryno- and herpesvirus. They are closely related to human respiratory tract diseases causing development of ARVI [5] in human being.

According to a Unified Clinical Protocol for Primary Health Care (UCPPHC) for adults and children "Acute respiratory infections" (MOH of Ukraine, order number 499 of 16.07.2014) include following diseases of upper and lower respiratory tract [6]

- J00 - Acute nasopharyngitis (rhinitis).
- J01 - Acute sinusitis.
- J02 – Acute pharyngitis.
- J03 - Acute tonsillitis.
- J04 - Acute laryngitis and tracheitis.

- J06 - Acute upper respiratory infections of multiple localization.
- J20 - Acute bronchitis.
- J21 - Acute bronchiolitis.
- J22- Unspecified acute respiratory infections of the lower respiratory tract

Influenza is one of the representatives of ARVI too but unlike usual ARI its effects are more frequent and have difficult complications. Therefore, the first symptoms of disorder in respiratory systems require getting special attention from doctor because it is necessary to detect influenza in time.

In Ukraine for diagnosis and treatment of influenza in adults and children there is recommended Clinical Protocol which unifies primary, secondary (specialized) medical care for adults and children in case of this disease. Most ARVI have seasonal background. The highest recorded level of these diseases takes place in autumn, winter and spring and enterovirus blooms in spring and summer. Infectious diseases of upper respiratory tract spread easily and their development is characterized by general intoxication syndrome mainly affecting mucous membranes of respiratory tract.

For example, rhinoviruses affect nasal mucosa, parainfluenza - larynx and trachea and influenza - trachea and bronchi. Lack of opportunities to use specific etiological diagnostic methods for defining real cause of respiratory disease in each case do not give opportunity to reveal real level of acute respiratory viral infections (ARVI) and separate them from illnesses of other ARI etiology: legionella, mycoplasma, coccia, rickettsia or etc.

The spread and frequency of these diseases in the world, which create global epidemic process affecting a large number of people time to time, usually lead to considerable economic losses. Empirical antibacterial treatment is used in case of ARI in Healthcare Establishments (HE) which provide primary care. Preference is given to oral forms of antibacterial drugs which are active against the most frequent pathogens of respiratory system (topical diagnosis - pharyngitis, otitis etc.).

To prevent dysbiosis in children prescription of antidiarrhea drugs-A07FA

Enterozhermina, Linex, etc.- are recommended. Symptomatic therapy is aimed at taking out and correction of ARVI symptoms such as: fever, headache, sore throat, ear pain, nasal congestion, rhinorrhea, cough etc.

Symptomatic pharmacotherapy significantly improves health quality of patient. Drugs applicable for medical correction of these symptoms in children include: NSAIDs-M01A E (ibuprofen, mefenamic acid), analgetics-antipyretics-N02B E (paracetamol, metamizole sodium), sympathomimetic-R01AA (oxymetazoline, xylometazoline), local antiseptics for throat treatment - R02AA (phenol, ambazone, dekvalinium chloride), antihistamine drugs for systemic use -R06A (loratydine, desloratadine), expectorants-R05CA (althea root, ivy leaves, thyme drugs, licorice root), mucolytic agents-R05SV (ambroxol and their combinations).

A significant number of these drugs used in combination therapy are aimed at improvement of several disease symptoms. Although ARVI are known to be caused by viruses, there is no reliable information on the effectiveness of antiviral drugs that are registered in Ukraine. Thus, antiviral medications for "Acute respiratory infections" [6] are not recommended for the treatment of ARVI in adults and children on regular basis (except «Oseltamivir» and «Zanamivir for influenza treatment).

Wide spread of ARVI diseases and high cost of their treatment show their medical and socio-economic importance for society and creates need for proving pharmacoeconomic approaches for drugs choice in pharmacotherapy of children patients.

The analysis of recent researches and publications provided on this topic have showed that main efforts are focused on research of clinical and economic backgrounds for pharmacotherapy of treatment ARVI diseases in children. But no special attention was paid to analysis of ARVI of children's pharmacotherapy costs provided by Ministry of Public Health of Ukraine by National Drug Formulary of Ukraine (NDFU) and Unified Clinical Protocols for Primary Health Care (UCPPHC) in adults and children with acute respiratory infection (ARI).

The above mentioned reason demonstrates need for analyzing of compliance of existing state of things with prescribed drugs regulations in pharmacotherapy of patients. Results of this analysis along with quality of pharmacotherapy allow to determine level of formulary system in studied Healthcare Establishments (HE).

Aim of this work has been clinical and economical analysis of clinical practice in real life of hospital environment in Sumy regiUkraine, as for pharmacotherapy of children with ARVI desiases on basis of Integrated ABC / VEN / Frequency analysis for its compliance assessment with modern standards of pharmacotherapy and for optimization pharmacotherapy costs.

Materials and Methods

To achieve this goal it was necessary to perform following tasks: to carry out retrospective analysis of prescription lists in patients with ARVI; to determine frequency of drugs prescriptions to patients with ARVI; to estimate compliance of ARVI therapy with regulatory documents of MOH Ukraine on results of formal VEN-evaluation analysis.

This analysis takes into account presence of drugs in the National Drug Formulary of Ukraine (NDFU) (7 th, 8th issues) [7, 8], Protocols of Treatment of patients with ARVI and related diseases [6]. Results of ABC-analysis determine structure and rationality of ARVI therapy costs [9]. To calculate value of particular drug treatment the average price of used packaging drug administered in patients with ARVI was taken into account in pharmacy network in Ukraine during study period (May-June 2018).

Children's disease cases with ARVI treated in children's department of the central district hospital in Burin town, Sumy region 2015-2016 were analyzed for quality assessment of pharmacotherapy. 180 prescriptions and disease cases of "acute respiratory viral infection" were analyzed on following criteria: number of cases, gender and age of sick children, duration of hospital treatment, number of prescribed drugs to one sick child, amount of related diseases.

Results and Discussion

Quantification of disease cases in children with ARVI shown in Table 1.

Table 1: Characteristics of children's with ARVI medical histories

The analyzed indicators	Total	
Number of disease cases	180	
Gender of patients (number of patients and in%)		
Girls	82	
Boys	98	
The age of patients	Minimum age - 6 months	maximum age - 17 years
Duration of being in hospital (days)		
Maximum	16	
Minimum	4	
On average	8	
Number of prescriptions drugs one patient (units).		
Maximum	12	
Minimum	5	
On average	7	
Number of related disease (units).		
Maximum	3	
Minimum	1	
On average	2	
Number of prescribed drugs		
INN (International Non-patental Name)	54	
TN (trade name)	95 drugs and 1 dietary supplement	
Pharmacotherapeutic group	30	
Total number of drug prescriptions	1241	
Total amount of money spent	106 940.19 hrn.	

Along with ARVI doctors often indicate diseases in local respiratory system such as: acute rhinosinusitis (124 patients), acute media otitis (21 patients), acute pharyngitis (18 patients), acute laryngitis (10 patients). Apart from main disease some concomitant illnesses are presented in disease cases: ulcerative colitis (4 patients), chronic gastroduodenitis (3 patients), acute intestinal

infection (3 patients). According to research conducted no sick child has been diagnosed with "Influenza" that allowed to provide clinical and economic analysis among adults and children with acute respiratory infections with drugs not included in clinical protocol for influenza by UCPPC. Gender content of research: 98 patients were boys (54.4% of total patients) and 82 girls (45.6%

of patients). Minimum age of children was 6 months, maximum - 17 years. Staying duration in hospital from 4 to 16 days. Average duration of being in hospital - 8 days. Average number of prescription made for one sick child - 7 (minimum amount - 5; maximum - 12). Such data indicate that doctors in this hospital practice polypragmacy. Number of drug prescriptions performed is evidence of severe course of disease or presence of concomitant disease.

Polyadministration of many drugs at a time requires special attention because undesirable interactions of drugs can lead to side effects. Analysis of primary data from prescription lists revealed that 95 Trade names (TN) of drugs (54 International not patent names - INN) and 1 Dietary Food Supplements belong to 30 pharmacological groups. All drugs named above were used in the treatment of 180 children with ARVI. These drugs were prescribed 1,241 times. Correlation between domestic and imported drugs was 1:1. Amount of money equal to 106 940.19 hrn. Was spent on pharmacotherapy of patients in Burin.

Clinical and economic analysis of children's disease cases gave possibility to estimate rationality of prescribed drugs and money spent. The first stage of clinical-economic analysis was assessment of necessity of drugs prescribed for children's therapy based on results of formal VEN analysis according to health regulations: NDFU (7 and 8 issues) [7, 8] and UCPPHC for adults and children [6].

Nowadays pharmacotherapy of patients must meet standards of treatment and drugs prescribed in case of their presence in National Drug Formulary of Ukraine. Drugs were divided into 2 groups: vital-essential (group V) and secondary - non-essential (Group N) for VEN formal analysis.

The results showed that 56 drugs TN (58.33%) out of 96 drugs prescribed to NDFU belonged to 27 INN (50%) and 40 TN were not included in this regulatory document. Decreased level of NDFU pharmacotherapy can be explained by frequent prescription of drugs with low probative effects (herbal antiviral, antidiarrheal and homeopathic remedies, etc.). 28 INN out of 54 (51.85%) of total amount of prescribed drugs were included in UCPPHC for adults and children with ARVI.

The low rate of compliance with pharmacotherapy UCPPHC is associated with small amount INN included in composition of medical regulatory documents. After careful analysis it was found that 26 INN drugs are not included in UCPPHC in adults and children with ARI, and 12 out of 26 INN drugs are recommended by UCPPHC to patients with related diseases: 3 INN for patients with chronic gastroduodenitis [10], 5 INN for patients with acute intestinal infection [11] 4 INN for patients with ulcerative colitis [12].

That is why 14 INN drugs were absent in all analyzed clinical protocols and they were put to group N - non-essential drugs. Doctors prescribed some of them to children. These drugs were antiviral agents (3 INN), homeopathic products (2 INN), adjuvants, such as interferons (2 INN drugs), vitamins and minerals (2 INN), dietary supplements (one product) and other. Among all drugs studied only 8 INN were included in NDFU and 13 INN were included in UCPPHC for patients with ARI, 3 INN were included in UCPPHC for patients with chronic gastroduodenitis, 5 INN were included for patients with acute intestinal infection and 4 INN for patients with ulcerative colitis. At the same time 17 INN were included in UCPPHC and NDFU and 4 INN from 6 pharmacological groups were absent in both Health Regulatory documents (Table 2).

Table 2: Non essential drugs not included in Health Regulatory Documents - NDFU (7 and 8 issues) and Clinical Protocols

No p / p	Pharmacotherapeutic group (ATC code)	INN of drug	Trade name of drug, dosage form, manufacturer company (country)	% of prescriptions	% of cost
1	Complex homeopathic medicine (R05 X)	Comb drug	"Aflubin" drops 20 ml, Richard Bittner AG (Austria)	7.41	8.67
2	Antiviral medications for regular use (J05A X)	Enismium iodide	"Amizonchyk" Syrup 100 ml vial, "Farmak" (Ukraine)	2.16	5.48
			"Amizonchyk" Tablets 125 mg, № 20, "Farmak" (Ukraine)	1.12	0.92

3	Drugs that affect the nervous system (N07X X)	Glycine	"Glycine" Table. 100 mg, №50, Ltd. Arpimed Republic (Armenia / Ukraine)	0.97	0.06
4	Homeopathic remedies (L03AX15)	Comb drug	"Anaferon children" Tab. № 20 Materia Medica Holding Ltd. (Ukraine)	0.97	0.27
5	Cytokines and immunomodulators (L03A X)	Comb drug	"Immunoflazid" syrup 50 ml, Farmak (Ukraine)	0.08	0.11
6	Multivitamins with minerals (A11AA)	Comb drug	"Pharmaton® Vitality" Syrup 100 ml, Boehringer Inhel Khaimah International GmbH, Germany	0.08	0.15
		Multivitamins and iron	"Multyvitamol Dr. Theiss" solution for / per os., 500 ml Dr. Theiss Natur-Waren GmbH (Germany)	0.52	0.51
Total				13.31%	16.15%

Drugs with low evidence base: homeopathic remedies "Anaferon children" and "Aflubin", antiviral drug "Amizonchyk", immunomodulator "Immunoflazid", drug affecting nervous system - "Glycine" and 2 medicines from multivitamin pharmacotherapy group were not included to INN of both regulatory documents. All these non-essential drugs, except "Aflubin" and "Amizonchyk" were used seldom (2.62% of all prescriptions). Such drugs as "Aflubin" and "Amizonchyk" were prescribed to 136 patients (10.69% of prescriptions). Total costs spent on non-essential drugs were 17,227.21 hrn. (16.15% of total costs).

This money might be used more efficiently for vital essential drugs recommended by medical regulatory documents (NDFU and clinical protocols of treatment). Thus, the results of VEN formal analysis have shown that major part of prescribed drugs with TN (58.95 %) were included in NDFU (7 and 8 issues). It proves that doctors follow requirements of modern pharmacotherapy standards. It is "National Drug Formulary of Ukraine» state document, which is updated annually. Frequency analysis conducted on pharmacotherapy groups (PhT) and on trade names (TN) of drugs was next stage of this work.

To Top 10 prescribed drugs for children with ARVI were included: drugs for topical use of nasal cavity diseases (149 prescriptions), mucolytic drugs (120), homeopathy (109), interferon alfa -2b (81), III generation antibacterial drugs of cephalosporins (80), antiseptic drugs (61), non-steroidal anti-inflammatory drugs (69), antiviral agents (62), and the I-st generation of cephalosporins (45), antihistamines (42). Next, we compared 10 most prescribed PhT

groups with operating UCPPHC) for adults and children with ARI (2014). In this state document major groups and directions of pharmacotherapy are registered.

Results of comparison showed that 8 PhT group out of 10 most prescribed groups are included in UCPPHC and they can be used for pathogenetic and symptomatic treatment of ARVI. Homeopathic and antiviral drugs are not on this list. Thus, use of therapy in Burin hospital goes in line with requirements of current UCPPHC for adults and children with ARI by 80%.

Frequency analysis of TN showed what drugs doctors preferred. Top 10 drugs turned out to be: Nosol (94 prescriptions), Aflubin (92), Nazoferon (69) Septefril (52), Nurofen (53), Enterozhermina (52), Lazolvan (46), Cefazolin (34) Ceftriaxone (30) and Linex (29). Top-10 drugs made 80% of items (8 TN) that were advised by List of UCPPHC in adults and children with ARI.

Most often prescribed drugs: homeopathic remedy- "Aflubin" oral drops, 20 ml of Richard Bittner AG (Austria) production and interferon alfa-2b – "Nazoferon", nasal drops, 5 ml of Farmak (Ukraine) production were not included in UCPPC.

Though these drugs are quite safe even for children there is no solid evidence about their effectiveness. Thus, the results have shown that doctors followed clinical protocol requirements for ARVI treatment by 80%. Next stage of our study was to conduct ABC analysis of pharmacotherapy ARVI in children for revealing the most money consumption of TN and INN drugs. Results of TN evaluation conducted on basis of ABC analysis are shown in Table 3.

Table 3: Distribution of drugs into groups based on results of ABC analysis

Group	Number TN drugs	Amount, grn.	% drug costs
A	28	85669.79	80.11
B	23	15730.90	14.71
C	45	5,539.50	5.18
Total:	96	106 940.19	100

According to results of ABC analysis 28 TN drugs are included to group A, major part of it are: antibiotics, adjuvants, sympathomimetic, antiviral and expectorants. 23 medicinal products are included in Group B mostly presented by: antiseptic, antitussive, antihistamine, antimicrobial action. 45 TN drugs with

countervailing action are included to Group C. The most expensive is the group A which covers 80.11% of total expenditures. The question arose: "What was the reason for including drugs to group A: lots of prescriptions, or high cost of drugs?". To answer this question, we analyzed characteristics of Top 10 expenditure drugs from Group A (Tab. 4).

Table 4: Comparative characteristics of Top 10 in Group A for expensive and frequent prescriptions

Number / n	Brand name of drug, dosage form, the company manufacturers (country)	Price per package, hrn.	Average cost of drugs per treatment course for 1 child, grn	% of total costs	Frequency of prescriptions	% of prescriptions
1.	Emsef, solution for inj. 1000 mg №1, Emkyor Pharmaceuticals Ltd., (India)	79.00	1,106.00	10.38	10	0.81
2.	Aflubin, drops 20 ml, Richard Bittner AG (Austria)	99.24	99.24	8,56	92	7,41
3.	Lazolvan, solution for inj. №10, 15 mg / 2 ml, Boehringer Ingelheim Ellas AE (Greece / Ukraine)	270.39	135.20	5.83	46	3.71
4.	Amizonchyk, syrup 100 ml vial, Farmak (Ukraine)	32.92	197.46	4.90	29	2.34
5.	Nazoferon, nasal drops, 5 ml Farmak (Ukraine)	74.88	74.88	4.83	69	5.56
6.	Enterozhermina, caps. № 12 Yuniter Laboratories (France)	148.30	86.52	4.33	52	4.19
7.	Ceftriaxone-BHFZ sol. for inj. 1g №1, BHFZ (Ukraine)	12.38	148.56	4.16	30	2.42
8.	Ceftriaxone-BHFZ sol. for inj. 500mg №1, BHFZ (Ukraine)	9.20	110.40	3.70	36	2.91
9.	Nurofen, Tab. 400 mg №12, Rekkitt Helsker Benckiser (Ve-lykobrytaniya)	71.72	71.72	3.55	53	4.27
10.	Canephron N, drops 100 ml, Bionorica SE (Germany)	189.27	189.27	3.00	17	1.37

4 of 10 leading drugs from group A turned out to have high percentage of prescriptions. They were: "Aflubin", "Nazoferon", "Enterozhermina", "Nurofen" (1, 5, 6 and 9 positions, respectively). Other 6 drugs have been attributed to this group due to high cost of course treatment. The final stage of clinical and economic analysis of children with ARVI pharmacotherapy was comparison results that were obtained in each stages of research. Integrated ABC / VEN analysis helped to understand efficiency of resources

used in hospital which was under investigation. The comparison of ABC and VEN analysis by NDFU (Fig. 1) showed that 12 TN from Group A (42.85%) were with criterion «N». They were not in NDFU and they were not recommended for use. Costs for these secondary drugs were 35771.50 hrn. (33.45% of total costs). In Group B 11 TN with «N» criterion 5122.44 hrn. (4.79% of total costs) were spent. In group C 17 TN with «N» criterion 2192.27 hrn. (2.05% of total costs) were spent.

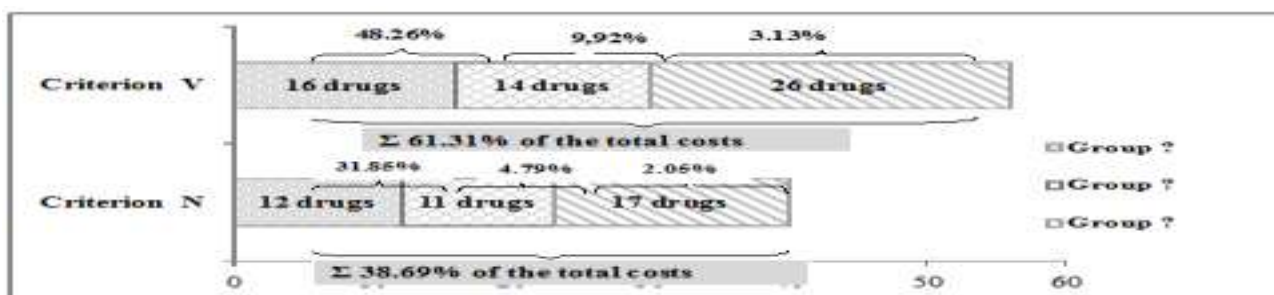


Fig. 1: Comparison ABC / VEN analysis according to NDFU Ukraine (7, 8 issues)

Thus, we can conclude that 45086.21 hrn. - 42.16% of all money spent for 40 non-essential drugs were used irrationally according to National Drug Formulary of Ukraine. These non-essential drugs were prescribed 562 times (45.33% of total 1241 prescriptions).

The comparison of ABC and VEN-analysis conducted by UCPPHC in adults and children with ARI and clinical protocols for treatment of opportunistic infections in children have shown that a group of non-essential drugs 14 out for 54 INN - were with «N» criterion. 6 TN with general expenses 22,927.98 hrn. (21.44% of total costs) to group A were attributed. In group B for 2 non-essential drugs 1,443.69 hrn. (1.35%) were spent. In group C for 11

non-essential drugs 1,475.77 hrn. (1.38%) were spent. All 19 non-essential drugs (19.79%) were prescribed 300 times (24.17% of total prescriptions). General costs have been 25,847.44 hrn. (24.17% of total expenses) (Fig. 2). 6 TN drugs based on 4 INN and prescribed 165 times (13.31%) were not included in both Medical Regulatory Documents. Their costs were 17270.08 hrn. (16.15% of total cost patients pharmacotherapy). Thus, optimization of children with ARVI pharmacotherapy in Burin town, Sumy region requires reducing of non-essential drugs prescription due to requirements of: NDFU (7 and 8 issues) and UCPPC for adults and children with ARI and related diseases.

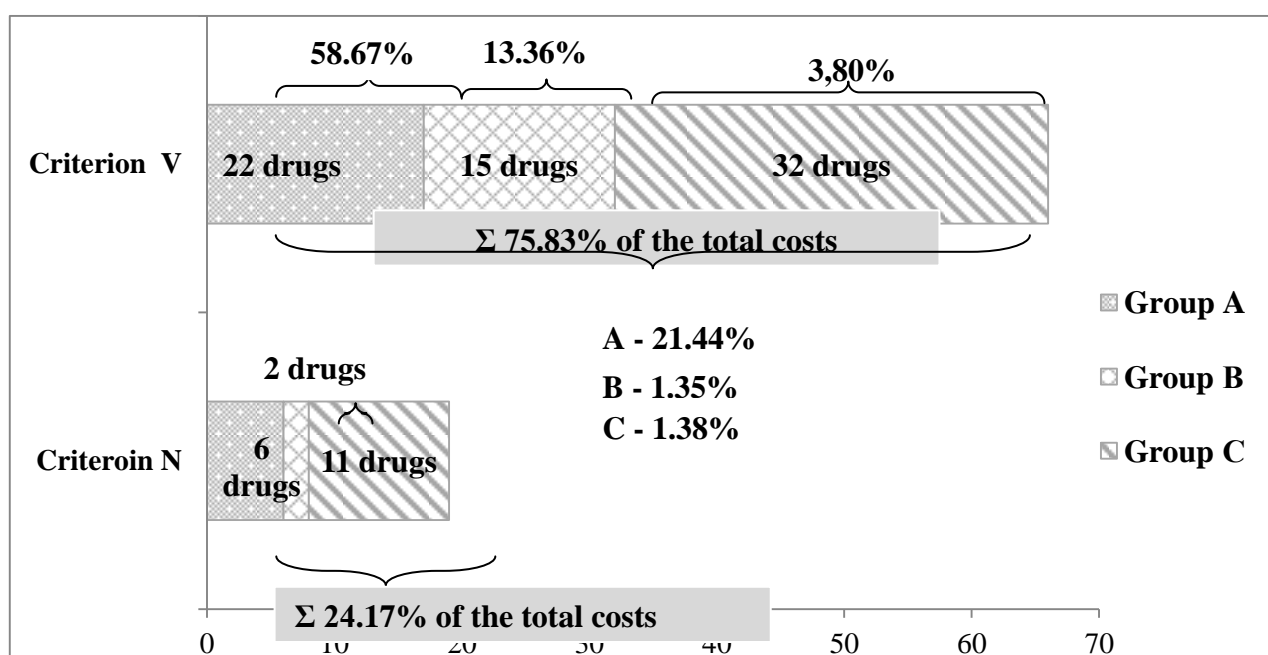


Fig. 2: Comparison ABC / VEN analysis according NDFU adults and children with ARI (2014)

Conclusion

- According to the clinical and economic analysis, main ARVI pharmacotherapy in children meets requirements of Unified Clinical Protocols for Primary Health Care (UCPPHC) for adults and children with acute respiratory infection on the whole in studied health institution.
- Integrated ABC / VEN / frequency analysis has highlighted need for adjusting of ARVI pharmacotherapy in children to NDFU to increase financial rationality. Reason is that out of 96 prescribed drugs 40 drugs were not included in NDFU (7 and 8 issues). 19 drugs were not included in UCPPHC for adults and children with ARI. Drugs mentioned above were not included in Pre-clinical Protocols for patients with

concomitant diseases too. 6 drugs were not included in both Health Regulatory Documents. Non-essential drugs were not included in NDFU, UCPPHC and they were prescribed 562 times (45.33%), 300 times (24.17%) and 165 times (13.31%). The total expenditures on concomitant therapy turned out to be: 38.69%, 24.17% and 16.15% respectively.

- Optimization of pharmacotherapy of children with ARVI and decrease of financial coverage of costs spent on treatment in Burin town can be provided via exclusion of homeopathic remedies "Aflubin" and antiviral drugs "Amizonchik" (syrups and tablets) from treatment schemes because they are not on clinical protocols of NDFU drugs and have high price.

- Total cost of these drugs turned out to be 1648.69 grn. (15.07%).

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