Availability of pediatric-evaluated formulations in Serbia

Bojana Božić¹, Sanja Stupar², Duško Stupar³, Uroš Babić⁴, Milica Bajčetić¹,⁵

Abstract:
OBJECTIVES: The aim of this study is to analyze the availability and coverage by health insurance reimbursement of pediatric formulations labeled for children up to the age of 12 in Serbia. To provide good insight in general availability of pediatric medicines, results were compared with the World Health Organization’s (WHO) “Model List of Essential Medicines for Children” and with published evidence.

MATERIALS AND METHODS: Sources of information about medicines are the Summary of Product Characteristics, National Health Insurance Fund (NHIF) Drug Lists, WHO Model Lists of Essential Medicines for Children, and Serbia’s official drug registry (2013).

RESULTS: Out of total number of medicines in Serbia, only 49% (496) were available for children. Of all available drugs for children, 66% were with license and majority were parenteral formulation (57%), followed by drugs for local use (28%) and formulations for oral use (23%). The lowest availability of medicines was for children 0–27 days. From the total number of licensed medicines for children up to 12 years old, NHIF covers 64% of drugs. The availability of the WHO essential medicines for children in Serbia was 51%, from which 92% were licensed for pediatric use.

CONCLUSIONS: Our results demonstrated the alarming lack of pediatric suitable formulations in Serbia. Significant differences in the availability of drugs suitable for children exist worldwide. From global health point of view, the differences in the access to children formulations should, therefore, be of the highest priority.

Keywords: Availability, children, essential medicines, license, medicines

Introduction

A lack of appropriately authorized medicines for the pediatric population is a major problem as it often leads to inadequate treatment of children.[¹] This problem is global and universally affects children in developing and developed countries.[²‑⁷]

One of the limiting factors for access to medicines in the pediatric population is the availability of oral formulations that are suitable for children. A study conducted in Serbia, the USA, and Germany showed that significant country-to-country differences continue to exist in both of the number and type of oral drug formulation that have pediatric labeling.[⁸] Since neonates and young children are not able to swallow tablets and capsules, lack of suitable oral formulations’ medicines has major consequences. One of the consequences is preparation of medicines extemporaneously in local pharmacies.[⁸,⁹] This kind of children’s treatment is considered as unacceptable because efficacy and safety of these products has never been evaluated. Furthermore, intravenous drugs are often too concentrated and therefore not suitable for the neonates and young children use without modification.[⁸]

A broader approach should be used to better describe the total availability of pediatric formulations worldwide. In addition to
licensing and labeling, the cost of the medicines and reimbursement by health insurance coverage also determine accessibility.

Although great progress has been made over the past few decades in resolving some ethical, technological, and scientific problems in pediatric pharmacology, little success has been seen in improving the availability of medicine for children.[2]

Pioneering legislation on pediatric medicines came into force in the United States in 1997.[10] In 2007, European Union’s Paediatric Regulation was adopted with the aim to promote the development and improve the availability of medicines for children of all ages, ensure high quality of medicines, and provide the information about the safety, effectiveness, and dosage of drugs for the pediatric population.[2]

In the same year, the World Health Organization (WHO) published the first “Model List of Essential Medicines for Children” and started the campaign “Make Medicines Child Size” to raise awareness about the global problem affecting pediatric therapy. With the relatively recent implementation of these initiatives, we do not immediately expect a complete resolution of the problem of “therapeutic orphans,” yet we believe that enough time has passed for initial concrete results.[10]

The aim of this study is to analyze the availability and coverage by health insurance reimbursement of pediatric formulations labeled for children up to the age of 12 in Serbia. To provide good insight in general availability of pediatric medicines, results were compared with the WHO’s “Model List of Essential Medicines for Children” and with published evidence.

**Materials and Methods**

We conducted a pharmacoepidemiological study analyzing the availability of pediatric formulations labeled for children up to the age of 12 in Serbia. In Serbia, complete pediatric population up to 18 years of age has free mandatory health insurance coverage. Drugs are classified according to Anatomical Therapeutic Chemical Classifications. Primary sources of information about medicines (license, drug formulation, and for which age of children is advised) are the Summary of Product Characteristics, National Health Insurance Fund (NHIF) Drug Lists, WHO’s “Model Lists of Essential Medicines for Children,” and Serbia’s official drug registry (2013).[11-13]

Children were divided into the following age groups: newborn infants (0–27 days), infants and toddlers (28 days to 23 months), and children (2–12 years). In this study, medicines for children under the age of 12 are categorized as: oral formulations (liquid formulations for oral use, such as suspensions, syrups, drops, elixirs and juices, drugs for chewing and sucking, drugs that are melting and dissolving, powders, or granules), parenteral formulation, and formulations for rectal, nasal, or local use. Extemporaneous formulations are excluded from this study. From the essential list of medicines, we did not analyze diagnostic agents, disinfectants and antiseptics, preparations for oral rehydration, solutions for peritoneal dialysis, or solutions for fluid, electrolyte, and acid-base balance compensation.

**Results**

In the Republic of Serbia (RS) in 2013, out of 1015 International Nonproprietary Names, 496 (49%) drugs were suitable for pediatric use. During the same year, of all drugs available to the pediatric population, 66% were licensed for pediatric use [Table 1]. Of all licensed drugs, the majority were drugs from the category of parenteral formulations (57%), followed by drugs for local use (28%) and formulations for oral use (23%). Drugs were least available for the age group of 0–27 days (4.7%), followed by the age group of 28 days to 23 months (26%) and finally by the age group of 2–12 years (45%).

The highest percentage of licensed medicines is in the category of antiparasitic drugs (100%) and anti-infectives for systemic use (89%). The lowest percentage of licensed drugs is in the categories of antineoplastic and immunomodulating agents (34%) and medicines for

**Table 1: The percentage of available licensed medicines for children up to 12 years old in the Republic of Serbia**

| ATC classification | Availability (number of medicines) | License, number of medicines with license (%) |
|--------------------|-----------------------------------|---------------------------------------------|
| A - Alimentary tract | 67 | 48 (72) |
| B - Blood and blood-forming organs | 31 | 20 (65) |
| C - Cardiovascular system | 12 | 6 (50) |
| D - Dermatologicals | 40 | 21 (53) |
| H - Systemic hormonal preparations | 15 | 11 (73) |
| J - Anti-infectives for systemic use | 93 | 83 (89) |
| L - Antineoplastic and immunomodulating agents | 59 | 20 (34) |
| M - Musculoskeletal organs | 23 | 9 (39) |
| N - Nervous system | 56 | 39 (70) |
| P - Antiparasitic products, insecticides, and repellents | 2 | 2 (100) |
| R - Respiratory system | 47 | 37 (79) |
| S - Sensory organs | 38 | 20 (53) |
| V - Others | 13 | 10 (77) |
| Total | 496 | 326 (66) |

ATC=Anatomical Therapeutic Chemical
the musculoskeletal system (39%). In nine therapeutic subgroups, no drugs were licensed for children: drugs for use in the therapy of hepatobiliary disease A05, antihypertensive drugs C02, emollients and protectants D02, antipsoriatic drugs D05, drugs for the treatment of bone diseases M05, other drugs for disorders of the musculoskeletal system M09, psychoanaleptic drugs N06, otologicals S02, and ophthalmological and otological preparations S03.

From the total number of licensed medicines for children up to 12 years old, 64% of drugs were reimbursed by NHIF [Table 2]. In each therapeutic group, at least one medicine is covered by NHIF.

The availability of essential medicines from the WHO’s list for children in Serbia was 51%, from which 92% were licensed for pediatric use. Drugs for neonatal care and antimigraine medicines from the WHO “Model List of Essential Medicines for Children” were not available in Serbia [Figure 1].

### Discussion

The present study shows that only 49% of medicines are suitable for children, of which 66% are with license. Despite the growing number of new medicines on the world market, the total availability of licensed drugs for children differs clearly between countries (New Zealand 35%, Australia 38%, the Netherlands 48%, the USA 54%, and the United Kingdom 59%).[5‑7] In addition, despite the fact that in the China, pediatric population accounts 20% of total population, pediatric medicines accounted for only 2% of the total medicines available.[14] All of these data are indicating that inadequate number of licensed drugs for children is a global phenomenon.

| ATC classification                  | Licensed (number of drugs) | NHIF (%) |
|-------------------------------------|-----------------------------|----------|
| A - Alimentary tract and metabolism | 48                          | 19 (40)  |
| B - Blood and blood-forming organs | 20                          | 12 (60)  |
| C - Cardiovascular system           | 6                           | 3 (50)   |
| D - Dermatologicals                 | 21                          | 10 (48)  |
| H - Systemic hormonal preparations  | 11                          | 7 (64)   |
| J - Anti-infectives for systemic use| 83                          | 64 (77)  |
| L - Antineoplastic and immunomodulating agents | 20 | 19 (95) |
| M - Musculoskeletal system          | 9                           | 8 (89)   |
| N - Nervous system                  | 39                          | 27 (73)  |
| P - Antiparasitic products, insecticides, and repellents | 2 | 1 (50) |
| R - Respiratory system              | 37                          | 18 (49)  |
| S - Sensory organs                  | 20                          | 18 (90)  |
| V - Others                          | 10                          | 4 (44)   |

ATC=Anatomical Therapeutic Chemical, NHIF=National Health Insurance Fund

Figure 1: The availability of essential medicines from the World Health Organization’s list for children in Serbia
Tablets and capsules are generally considered suitable for older children while melting and chewing tablets are more likely to be taken at a younger age. However, the availability of suitable oral formulations for children is limited not only in our country but also worldwide.\textsuperscript{4,8,14} Recently, published study showed the total absence of labeled age-appropriate oral formulations for cardiovascular treatment in children.\textsuperscript{8} Limited availability of suitable oral formulations leads to improvisation of their administration, with unknown consequences.\textsuperscript{8} Great progress has been made by introduction of fast-dispersing tablets since they facilitate the administration of low doses. Developing and evaluation of enalapril age-appropriate solid oral formulation for all pediatric subsets is the framework of Labeling of Enalapril from Neonates up to Adolescents project, funded by the European Commission’s Seventh Framework Programme.\textsuperscript{13} To improve situation on the pediatric drug market, European Union funding projects are directed to development and evaluation of novel formulations.

Similarly, as results from other countries, our study showed that the lowest availability of licensed drugs is for the youngest children.\textsuperscript{3,5,6} Studies from the USA showed a higher number of licensed drugs for children compared to New Zealand and Australia, but no statistical differences in number of licensed drugs for the youngest children is observed between these countries.\textsuperscript{16,17} One of the possible explanations is the fact that this part of the pediatric population is particularly hard to conduct clinical trials.

To estimate in which therapeutic areas problems are present in clinical practice, it is also important to evaluate prescription patterns in pediatric population. A study conducted in Italy, the Netherlands, and the UK showed that the most often prescribed drugs for children are anti-infectives, dermatologicals, and respiratory drugs. Drug classes such as cardiovascular, antiparasitic, hormonal, antineoplastic, and musculoskeletal have a low prevalence of prescription.\textsuperscript{18} Our results showed that percentage of licensed drugs varies widely, from antiparasitic (100%) to antineoplastic and immunomodulating agents (34%). Such data are not unique for our country. Results from the Netherlands showed that the highest percentage of authorized medicines for children has antiparasitic products, insecticides and repellents (89%), anti-infectives for systemic use (86%), drugs for respiratory system (86%), and the lowest percentage drugs for genitourinary system and sex hormones (11%).\textsuperscript{4} A study that compared results gained from the USA, New Zealand, Australia, and the UK showed a low prevalence of licensed antineoplastic and immunomodulating agents, cardiovascular, and drugs for the musculoskeletal system.\textsuperscript{16} Great discrepancy in the number of licensed and available drugs between therapeutic classes could be explained with the fact that certain diseases are relatively rare in children’s age, so pharmaceutical companies do not have interest to invest money in extensive clinical trials.\textsuperscript{9} This is a possible explanation for unsatisfactory number of licensed cardiovascular medicines for children even in developed countries such as Germany and the USA.\textsuperscript{8,16} The degree of licensed vaccines for children is far better because of certain economic refund.\textsuperscript{20} Quite alarming results from our research are existence of nine therapeutic subgroups in which there are no medicines licensed for children.

Certain medicines, although they are in everyday use, still do not have sufficient availability and authorization. In these cases, explanation is that beside financial side, often problems are ethical and technical issues in conducting clinical trials.\textsuperscript{8} Research that was conducted in Italy, the UK and the USA pointed that regardless of the prevalence of eye diseases and their possible consequences in the pediatric population, degree of medicines for eyes diseases is still insufficient. During 2010 in Italy, 48% of drugs for eye disorders were licensed, in the UK 64% and in the USA 54%.\textsuperscript{21} Similar results were obtained in our country; 56% of drugs for eye disorders were licensed for children.

Economic development of the country also has the impact on the availability of medicines for children. A study from 2010 showed existence of great differences in the availability of drugs that are used in children’s palliative care between countries, with the lowest availability of drugs in low-income countries.\textsuperscript{22} Another example of country with low income is India, where availability of medicines for children is not satisfactory in all therapeutic areas.\textsuperscript{23}

One of the major issues that can arise during the use of unlicensed medicines is their potential harmfulness for children.\textsuperscript{1} To improve the availability and the authorization of drugs, the WHO has created “Model Lists of Essential Medicines.”\textsuperscript{15} Disappointing data is that in RS, availability of medicines from the WHO Essential List is only 51%, and of those drugs, 92% are licensed. Certain drug groups, such as antimigraine and specific drugs for neonatal care, do not have any registered medicine on the market while drugs that affect the respiratory system and blood products and plasma substitutes have 100% availability. These data can be compared with other countries. The availability of drugs compared to the WHO “Model List of Essential Medicines” in Sri Lanka was 52% and in public tertiary hospitals in Guatemala 46% (range from 28% to 56%).\textsuperscript{24,25} The availability of essential medicines according to WHO in 14 countries in Central Africa, was between 38% and
62% depending on the country. In Africa, variation of the availability of medicines for priority diseases, such as HIV infection, tuberculosis, and malaria, was alarming.\(^ {26}\)

From total number of licensed medicines for children up to the age of 12 years in our county, NHIF covers 64% of medicines, and from each therapeutic group, at least one medicine is reimbursed by fund. Since RS is country with low income, higher expectations at the moment are not realistic.

### Conclusions

The development of new drugs, especially suitable oral pediatric formulations, is a great challenge in modern clinical pharmacology. Although expectations that all drugs for adults are available for children are not realistic, today unsatisfactory availability and a low number of licensed drugs for the pediatric population represent a cause for concern and suggestion for much-needed research. The attention should be focused to all therapeutic groups. To improve availability and to achieve better affordability, the government should create a list of national essential medicines.

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### Conflicts of interest

There are no conflicts of interest.

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