

How to choose an appropriate drug dosage form for the treatment of respiratory infections in children: Facts and tips

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Abstract

The treatment of respiratory infections in children requires special attention, since the paediatric population has rather specific characteristics and consists of heterogenous subgroups. In this context, the choice of a suitable drug dosage form is of particular importance, depending on the active substance properties, along with the age and general condition of a paediatric patient. The most commonly used pharmaceutical products for respiratory infections in children include oral, parenteral and inhalation dosage forms, although a large number of drugs are not available in a suitable dosage form and/or strength for paediatric age, leading to the frequent use of unauthorized drugs (i.e., unlicensed use). Other important issues that should be considered when choosing the appropriate paediatric dosage form and/or compounding procedure are related to the careful considerations of the pharmaceutical product composition (safety of excipients) and the choice of administration/dosing device in relation to a child's age.

This paper provides an overview of paediatric dosage forms used in the treatment of respiratory infections in children, their benefits and limitations. The review includes examples of various pharmaceutical products, along with the considerations regarding administration/dosing devices. Specific characteristics of paediatric populations affecting the decision on the choice of age-appropriate paediatric formulation are also addressed.

Key words: paediatric dosage forms, age-appropriate formulation, extemporaneous compounding, administration/dosing devices, respiratory infections

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Introduction

The prevalence of acute respiratory infections (ARIs) among children is rather high. About 50% of children's visits to physicians are caused by ARIs, including infections of the nose, sinuses, throat, larynx, ear and lungs (1). Moreover, according to the World Health Organization (WHO), more than 2 million of children die from ARIs each year, prevalingly from pneumonia in developing countries (2). In general, lower respiratory tract infections are more severe, especially in younger children, and are the leading cause of death in children under 5 years (3).

ARIs are mostly caused by viruses, but bacterial infections are also common in children. Regardless of the etiology, most ARIs require the use of medicinal and/or supportive medicinal products, either for causative or symptomatic therapy. Commonly used drugs for ARIs include mucolytics/expectorants, antibiotics, bronchodilators, corticosteroids, antihistamines, antipyretics, nasal decongestants etc., along with supportive therapy with vitamins and other dietary supplements/medical devices. These drugs/active ingredients come in different formulations/dosage forms, and appropriate selection of a dosage form can be one of the key determinants for a successful therapy, especially in the paediatric population.

Specific characteristics of the paediatric population relevant for drug/dosage form selection

Choosing an optimal drug treatment for a sick child is not an easy task. It is well known that children are not "small adults", meaning that the paediatric population is distinct in many aspects. These include physiological characteristics, drug pharmacokinetics and pharmacodynamics, toxicity of drugs and excipients, desired/acceptable drug administration route, ability or willingness to take the medicine, desired taste/color/texture of a drug product, complexity of dose adjustment, etc. In addition, disease state may impact a drug bioperformance in a paediatric patient, and can also affect the ability of a child to take the medicine.

There are several criteria that may facilitate the selection of paediatric formulations/dosage forms, such as: disease state, paediatric age, safety of a drug substance/drug product (types and amounts of excipients, stability, risk of dosing error), ease of drug administration (a child's ability to take the drug, compliance, feasibility of accurate dosing, ease of administration by parents/caregivers/health workers), and the availability of a drug product (availability on the market, effective supply chain, price). In other words, a dosage form for a child needs to be age-appropriate. Unfortunately, only a limited number of drugs is approved for paediatric use, with even fewer drugs available in a suitable dosage form or strength for diverse paediatric age subsets. A decision matrix provided in the European Medical Agency (EMA) document "*Reflection paper: Formulations of choice for the paediatric population*" presents a good starting point in selecting an optimal drug dosage form in relation to paediatric age (4). For example, the matrix data on oral dosage forms indicate that liquid preparations are preferable for pre-

school children, dispersible dosage forms for school children, and solid dosage forms for adolescents (Figure 1); nasal preparations are generally acceptable (but not the dosage forms of choice), while preparations for inhalation can be a preferred choice for all paediatric age subsets, although this depends on the inhaler type.



Oral dosage forms	Pre-school children (2 – 5 years)	School children (6 – 11 years)	Adolescents (12 – 16/18 years)
Solutions/Drops	5	4	4
Emulsions/Suspensions	5	4	4
Effervescent dosage forms	5	4	4
Powders/Multiparticulates	4	4	5
Tablets	3	4	5
Capsules	2	4	5
Orodispersible dosage forms	4	5	5
Chewable tablets	3	5	5

Figure 1. An example matrix for the selection of oral dosage forms (4); the numbers denote codes/grades: 1 – not accepted/not applicable, 2 – provisionally accepted/applicable with problems, 3 – acceptable/probably applicable, but not preferred, 4 – preferred acceptability/good applicability, 5 – dosage form of choice/best and preferred applicability

Slika 1. Primer matriksa za odabir farmaceutskog oblika za peroralnu primenu (4); brojevi označavaju ocenu: 1 – neprihvatljiv/nemogućnost aplikacije, 2 – prihvatljiv sa rezervom/problematična aplikacija, 3 – prihvatljiv/mogući, ali nepoželjan način aplikacije, 4 – odgovarajuća prihvatljivost/laka aplikacija, 5 – farmaceutski oblik izbora/najpogodniji način aplikacije

Drugs and dosage forms in the treatment of ARIs in the paediatric population

The lack of authorized drugs in age-appropriate dosage forms often leads to unlicensed or off-label drug use in children with ARIs. In addition, drugs approved for adults are frequently manipulated to enable administration to a child (e.g., splitting or crushing of tablets), although such manipulation may lead to undesired effects (5). The EMA states that “manipulation of adult medicines for paediatric use should be the last resort, but at the same time it is recognized as an unavoidable and necessary operation in

many cases” (4). Therefore, for instance, the British National Formulary for Children (BNFC) provides information on unlicensed use of medicines and gives guidance on special orders and extemporaneous preparation (6). Recommendations regarding unlicensed use of paediatric medicines can also be found in certain hospital guidances or paediatric formularies, e.g., Guy’s and St. Thomas’, King’s College and University Lewisham Hospitals Paediatric formulary, 2012 (7). For example, it is stated there that intravenous administration of ribavirin is unlicensed in children, but can be used on expert advice in cases of severe infections with respiratory syncytial virus, parainfluenza virus, adenovirus, bronchiolitis or pneumonitis. The usage of epinephrine in children with croup is also an unlicensed indication, but the formulary provides recommendations on the use of nebulized solution for all paediatric age groups.

Literature data indicate that in 18.5% visits to ambulatory settings in the USA paediatric patients were prescribed with an off-label drug, mostly antihistamines and some antibiotics for upper respiratory tract infections (8). Another cohort study from the primary care facilities in the Netherlands demonstrated that 20.3% of prescriptions to children with respiratory diseases referred to off-label drug use (regarding age, dose, frequency, indication or dosage form), whereas 16.8% of prescriptions concerned unlicensed drugs (including modification/manipulation of adult medicines, use of drugs that lacked information on paediatric use, drugs contraindicated for use in children), and this trend was the highest among infants and toddlers (9).

One of the published reports on the prescription pattern regarding dosage form selection for children with ARIs indicate that oral dosage forms are the most commonly prescribed (42.3%), followed by inhalation (33.8%), parenteral (infusions, injections) (23.2%) and nasal dosage forms (0.7%) (10). However, the exact order may vary depending on the drug substance/drug therapeutic class, paediatric age, disease conditions and geographic region. For example, there is a report stating that the use of parenteral antibiotics in the paediatric population exceeds the use of oral preparations (11), while another report highlights the prevalence of oral antibiotic usage in children (syrups, capsules and tablets) (12). The trend of using oral dosage forms is likely to become even more pronounced, in line with the WHO recommendation that this route of administration should be the preferred one due to children’s better compliance, lower costs of treatment and lesser side effects in comparison to the parenteral route of administration (13, 14). Generally, parenteral preparations, e.g., intravenous and intramuscular injections, should be used in severe cases (e.g., severe pneumonia) and in paediatric indoor patients, especially newborns (13).

A review of the WHO Model list of essential medicines for children indicates that the availability of dosage forms, e.g., for antibiotic drugs used in the treatment of ARIs, is not fully in line with the needs of all paediatric age groups (15, 16). In addition, some age-appropriate formulations are not available in all countries (17). As a consequence, some medicines are given to children via wrong administration route (18). Therefore, there is an urgent need to develop new paediatric formulations suitable for children of different age groups.

Oral dosage forms

As mentioned above, oral dosing route is the preferred one for paediatric patients of all ages, and a number of authorized paediatric medicines used in ARIs are intended for oral administration. Liquid dosage forms, e.g., oral solutions, oral suspensions, oral emulsions, syrups and oral drops, are easy for use/swallowing in children and they provide good dosing flexibility, but their development and usage are associated with certain limitations: taste-masking and stability may present serious issues; certain excipients commonly used in oral liquid formulations should not be used or can be used in limited quantities in paediatric medicines (e.g., ethanol, propylene glycol, benzyl alcohol, parabens); dosing accuracy for some formulations may not be appropriate (and highly depends upon the choice of dosing device); and a single dosing volume (i.e., the volume of liquid medicine that contains a single drug dose) should fit the child's age, which is sometimes difficult to achieve (e.g., the recommended dosing volume for children below 4 years is limited to 5 ml) (19).

Solid dosage forms come in a great variety, including conventional (e.g., tablets, capsules, hard lozenges, powders, granules) and relatively novel dosage forms (e.g., sprinkles, orodispersible dosage forms, mini tablets, chewing gums, soft lozenges/troches, chewable lozenges/gummies, medicated lollipops). These dosage forms show better stability in comparison to liquid formulations, but the ease of administration and children's acceptability depend upon the type of dosage forms, e.g., the use of conventional tablets and whole capsules is limited by the swallowing ability of a child, whereas powders, granules, pellets and sprinkles for reconstitution are generally acceptable across all paediatric age groups. The acceptability of mini tablets, soft lozenges, gummies, chewable tablets and medicated lollipops is also very high among the paediatric population, but these products need to have good palatability (19). The examples of some age-appropriate oral dosage forms of paediatric drugs used in ARIs are described in Table I.

Table I Examples of oral preparations/dosage forms for drugs used in paediatric ARIs (6, 20-22)

Tabela I Primeri preparata/farmaceutskih oblika lekova za oralnu upotrebu koji se primenjuju kod akutnih respiratornih infekcija u pedijatrijskoj populaciji (6, 20-22)

Active ingredient (content)	Dosage form and excipients	Therapeutic indications	Notes
Dextromethorphan hydrobromide (10 mg/5 ml)	Oral solution Excipients: Sodium benzoate; citric acid anhydrous; liquid maltitol; saccharin sodium; propyleneglycol; strawberry flavour; contramarum flavour; purified water	Used for temporary relief of persistent dry cough caused by certain infections of the air passages (e.g., sinusitis, common cold)	Packed in single dose stick packs (5 ml); should be applied directly to the mouth, with no water required; for children from 12 years
Acetylcysteine (i. 200 mg) (ii. 100 mg)	i. Powder for oral solution* ii. Granules for oral solution* Excipients: i. Sucrose; ascorbic acid; saccharin; orange flavour ii. Sorbitol; aspartame; beta carotene; orange flavour	Used as a mucolytic adjuvant in the therapy of respiratory disorders associated with mucus hypersecretion	i. Packed in single dose sachets; for children from 12 years ii. Packed in single dose sachets; for children from 2 years
Ibuprofen (i. 100 mg/5 ml) (ii. 200 mg) (iii. 100 mg) (iv. 100 mg)	i. Oral suspension* ii. Orodispersible granules iii. Chewable tablets iv. Chewable capsules Excipients: i. Glycerol; sorbitol 70%, non-crystalline; xanthan gum; cellulose microcrystalline ii. Sodium benzoate; citric acid anhydrous; sodium citrate; saccharin sodium; sodium chloride hypromellose; xanthan gum; maltitol liquid; glycerol; lemon flavour; purified water iii. Acesulfame potassium; ammonium glycyrrhizate; aspartame; carnauba wax; croscarmellose sodium; D&C red 27 aluminum lake; FD&C blue 1 aluminum lake; hypromellose; magnesium stearate; mannitol; natural and artificial flavours, silicon dioxide; sodium lauryl sulfate; soybean oil; succinic acid iv. Gelatin; purified water; glucose, liquid; sucrose; fumaric acid; sucralose; citric acid; acesulfame K; disodium edetate; glycerin; natural orange flavour; red iron oxide (E172); yellow iron oxide (E172)	Used for the fast/effective reduction of fever and fast/effective relief of the symptoms of colds and influenza and mild to moderate pain, such as a sore throat	i. Packed in a bottle with child-resistant cap; contains a graduated oral dosing syringe; for children from 3 months ii. Packed in single dose stick packs; for children from 7 years iii. The tablet should be chewed or crushed before swallowing; for children from 2 to 11 years iv. The capsule should be chewed before swallowing; for children from 7 years

Active ingredient (content)	Dosage form and excipients	Therapeutic indications	Notes
Amoxicillin (1000 mg)	Dispersible tablets* Excipients: Magnesium stearate; aspartame; croscarmellose sodium; mannitol; talc; silicon dioxide, colloidal, anhydrous; cellulose microcrystalline; flavours (tablet core); aspartame; mannitol; maltodextrin; starch, soluble; titanium dioxide; talc (tablet coating)	Indicated for the treatment of bacterial respiratory infections (e.g., acute bacterial sinusitis, acute otitis media, acute streptococcal tonsillitis and pharyngitis, acute exacerbations of chronic bronchitis, community acquired pneumonia)	The tablets can be suspended in water before use or taken directly with a sufficient amount of water; they can be broken to ease the swallowing; dosing recommendations (refer to amoxicillin in general) based on a child's weight
Doxycycline hyclate (75 mg; 100 mg)	Delayed release capsules Excipients: Lactose monohydrate; microcrystalline cellulose; povidone; wheat starch; magnesium stearate; cellulosic polymer coating	Indicated for the treatment of bacterial respiratory infections	Capsules contain specially coated pellets; the capsules may also be administered by sprinkling the capsule contents on a spoonful of applesauce (applesauce should be swallowed immediately without chewing); for children from 8 years
Azithromycin (500 mg)	Granules for oral suspension Excipients: Gellan gum; sucrose; caramel aroma; aspartame; sodium phosphate tertiary anhydrous; medium chain triglycerides; mannitol	Indicated for the treatment of bacterial respiratory infections (e.g., bronchitis, community acquired pneumonia, sinusitis, pharyngitis/tonsillitis)	Each dose is packaged separately on a measuring spoon; for children weighing more than 45 kg
Paracetamol (250 mg)	Orodispersible tablets Excipients: Mannitol; crospovidone; aspartame; strawberry flavour; magnesium stearate; basic butylated methacrylate copolymer; polyacrylate dispersion 30%; colloidal anhydrous silica	Indicated for the treatment of mild to moderate pain and as an antipyretic; can be used in conditions like sore throat, colds and influenza	Tablet should be placed in the mouth where it melts on the tongue; alternatively the tablet can be dispersed in a teaspoonful of water or milk; for children from 6 years
Amylmetacresol/ 2,4-dichlorobenzyl alcohol (0.6 mg/1.2 mg)	Hard lozenges Excipients: Strawberry flavour; anthocyanins; saccharin sodium; tartaric acid; isomalt; maltitol syrup	Used as an antiseptic for the relief of sore throat and its associated pain	Lozenges should be dissolved slowly in the mouth; for children from 6 years
Pectin (5.4 mg)	Medicated lollipops Excipients: Caramel color; corn syrup; honey; natural flavor; sucrose; water	Used as an oral demulcent for sore throat	Lollipops should be allowed to dissolve slowly in the mouth; for children from 3 years
Diphenhydramine hydrochloride/ Phenylephrine hydrochloride (6.25 mg/2.5 mg)	Orodispersible films** Excipients: Acetone; FD&C blue 1; FD&C red 40; flavors; hypromellose; maltodextrin; mannitol; polyethylene glycol; polypropylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide	Used for temporary relief of runny/stuffy nose, itchy throat, airway irritation, cough and ear symptoms caused by common cold, flu, hay fever	Individually packed strips; the strip/film should be placed on the tongue where it melts quickly; for children from 6 years

* registered in the Republic of Serbia; ** discontinued product

An interesting paediatric-suitable dosage form is a sprinkle formulation (e.g., doxycycline hyclate delayed release capsules in Table I). Sprinkles come in the form of capsules intended to be open prior to use and their content sprinkled on a soft food. Therefore, this dosage form may be appropriate for children above 6 months. Particle size of granules or pellets in sprinkle capsules is one of the key formulation quality attributes, especially if they are designed to show modified drug release. Namely, the size of beads should not exceed 2.5 mm (23), because larger particles may trigger the chewing reflex, which may lead to abrupt drug release. Beside sprinkles, other dosage forms (e.g., powders, granules, crushed tablets, content from conventional capsules) are often mixed with food or drinks to allow easier administration to children. However, this practice should be used with caution, and only in cases when relevant data, e.g., information from Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPC), indicate that the medicine can be mixed with food/drinks. PIL and SmPC should also contain data on the type of food/drinks that the medicine can be mixed with, and information on whether chewing is allowed. Moreover, if mixing with food or drinks is unsuitable or has not been studied, appropriate warnings should be provided in the SmPC and PIL.

Other solid dosage forms recommended for use in the paediatric population are dispersible and orodispersible dosage forms, e.g. dispersible/orodispersible tablets. They are considered to be flexible dosage forms, and can be given either whole (to older children) or dispersed in water or breast milk (for younger children, even younger than 6 months) (14). Amoxicillin dispersible tablets listed in Table I are an example formulation of such a type. This drug has been recognized as an essential medicine for children (16), and in addition WHO recommended dispersible formulations of amoxicillin as the optimum formulation for paediatric patients with pneumonia (24). Amoxicillin is also available on the market in the form of hard capsules (250 mg, 500 mg), powder for oral suspension (250 mg/5 ml, 500 mg/5 ml), granules for oral suspension (250 mg/5 ml), oral suspension (125 mg/5 ml, 250 mg/5 ml) and powder for solution for injection (250 mg, 500 mg, 1 g) (20, 21), allowing flexible dosing via oral or parenteral route in different paediatric age groups.

A relatively novel type of oral formulation especially designed for use in children is the so called “pulp spoon” (prefilled teaspoon containing a single drug dose). The spoons, filled with powder or granules, are covered by micro-perforated foil and packed into separate bags. Prior to administration, the spoon should be taken out of the bag and dipped into a glass of water for e.g. 30 s, until the filling turns into a paste. After removing the foil, the child should swallow the paste immediately. Such formulations have a lot of advantages: e.g., their stability is high, the risk of spillage is low, they are easy to administer and allow precise dosing, and children’s compliance is high; however, they require specialized packing and may be difficult to formulate (5, 25). An example marketed formulation of this type refers to azithromycin granules for oral suspension on a measuring spoon (Table I).

Among the specific child-appropriate solid oral dosage forms, suitable for drugs used in ARIs, are also medicated lollipops. They can be manufactured at the industrial scale or compounded *ex tempore*. This dosage form is quite attractive for children because of the appearance (shape and color) and sweet taste (they can be flavoured as well), and suitable for use above the age of three. Moreover, they are a convenient option for patients who have difficulty swallowing (26). Lollipops can incorporate both locally and systemically active drugs used in ARIs (e.g., local anesthetics, antiseptics, antitussives, mucolytics, demulscents, analgetics), if they are heat stable and the taste can be successfully masked. The other concern regarding systemically active drugs is that drug dissolution and absorption rate may depend upon sucking intensity and saliva flow, which show large interindividual variations. An example commercially available formulation is shown in Table I.

As mentioned above, the ease of oral medicine administration and dosing accuracy highly depends upon the choice of administration/dosing device. Liquid medicines can be dosed with a measuring spoon, plastic cup, oral syringe, dropper or specially designed dispensers, such as modified feeding bottles (e.g., Medibottle[®]) or modified pacifiers. Oral syringes, droppers and special dispensers are favourable for infants and toddlers, while measuring spoons and cups are more suitable for older children. It is also important to note that a medicine should not be mixed with milk or formula in an infant's bottle because a child may refuse to finish the bottle and the drug will be underdosed. As for solid oral dosage forms, they can be administered either directly or via different dosing devices. For example, multiparticulate medicines like granules and pellets can be dosed by measuring spoons and cups, syringes for multiparticulate dosage forms (e.g., Sympfyny[™] multiparticulate delivery system) or drinking straws (e.g., XStraw[®]). Newly proposed administration/dosing devices for solid dosage forms include a nipple shield device (e.g., JustMilk delivery system) and a solid dosage pen (for extrudates), but they are still not commercially available on the market.

Nasal dosage forms

Drug delivery via the nose is normally considered to be suitable (although not favourable) for children of all ages, since it is a non-invasive route of administration (4, 27, 28). Intranasal delivery offers significant advantages that may allow a more efficient use of resources, more rapid patient care, and higher patient and provider satisfaction (29). Nasal preparations are usually used to treat diseases including nasal allergy, rhinitis, bacterial sinusitis, or nasal polyps in children (30). Since the nasal mucosa is richly vascularized, it provides fast and direct access to the systemic circulation and may be attractive as a needle-free alternative to invasive administration, especially when a fast onset of action (similar as with intravenous therapy) is essential (4, 30-32). In addition, a significant advantage of this route of administration is that there is no requirement for the medicine to be sterile (30). Furthermore, the nasal cavity is one of the most promising sites for mucosal vaccination (due to better systemic bioavailability compared with parenteral and oral administration) (30, 33). For example, Fluenz Tetra[®] vaccine nasal

suspension (AstraZeneca UK Ltd), licensed for prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age is available in European markets (6, 21).

Along with the above-mentioned advantages, there are certain disadvantages of this route of application. Significant absorption of active drug substances intended for local effect may increase the risks of systemic (adverse) effects. Moreover, the use of nasal preparations can cause temporary irritation of mucosa, which can be painful or produce a "runny nose" (4, 5, 34). The limited maximum volume per dose, usually being between 50 μl and 250 μl , depending on the device and formulation, is also an additional drawback (28), which requires special attention in the case of paediatric patients. Another interfering factor is children's compliance with the nasal administration route, which is generally rather low, especially in young children (35).

Nasal preparations include liquid (nasal drops, nasal sprays, nasal washes), semi-solid (ointments, creams, gels) or solid (nasal powders, nasal sticks) preparations and they are intended for administration to the nasal cavities to deliver active substances for a local or systemic effect.

During the development of a nasal preparation for the paediatric population, consideration should be given to whether there are documented differences between the anatomical and physiological characteristics of the nasal cavity of children and adults. Available literature data related to this issue is limited, and the characteristics of nasal mucus, nasal pH or mucociliary clearance are assumed to remain the same in children as in adults (19, 30). However, there is a recommendation that the maximum volume for a single administration into one nostril is 100 μl in neonates and 500 μl in older children, while there is no agreement about the volume that can be given to preterm neonates (29, 36). Nasal drops and nasal sprays are the most commonly used in the paediatric population. They are not recommended for administering highly potent (systematically acting) drugs, due to insufficient reliability in dosing characteristics. On the other hand, nasal drops may be preferred for infants, since their cavity is so small that one or two drops can cover the whole mucosa (4). Nasal washes are also often used in paediatric patients. They are generally aqueous isotonic solutions, intended for cleansing the nasal cavities. Nasal powders are less frequently used, but they are more stable compared to liquid formulations (30).

Nasal preparations may contain excipients, for example to adjust the tonicity or viscosity of the preparation, to adjust or stabilize the pH, to increase the solubility of the active substances, to stabilize the preparation, or to provide adequate antimicrobial properties. These excipients should not adversely affect the intended medicinal action of the preparation or, at the concentration used, cause toxicity or undue local irritation. During the development of a nasal preparation for the paediatric population, the formulation needs to be non-irritating (as far as possible), without adversely affecting the functions of nasal mucosa and its cilia (4, 37). The potential irritancy of highly concentrated solutions, especially if these are hypertonic, should be avoided (36). Penetration enhancers, if included in the formulation, should be proven as safe and

effective in the target population (4). In addition, palatability of paediatric nasal preparations may be one of the key factors influencing patient acceptability (27).

Preservatives are still the most important excipients related to safety concerns of nasal preparations used in children. Children are often exposed to benzalkonium chloride through nasal drops and nasal sprays containing, e.g., decongestants and corticosteroids. This excipient is usually considered to be safe, but it can produce bronchoconstriction, cough, pruritus, facial flushing and burning sensations in a dose-dependent manner (30, 38, 39). Since the concentration of benzalkonium chloride in nasal products for children from a multi-dose container is low, children are most likely not susceptible to the adverse effects of this preservative. In addition, single-dose containers can be recommended for children without the need to include preservative in the formulation (30).

Nasal drops are usually supplied in multidose containers with a suitable dosing device (4). Containers are made of glass or a suitable plastic material that is fitted with an integral dropper, or with a screw cap of suitable materials, incorporating a dropper and rubber or plastic teat (37). They can also be packed in squeeze bottles, but they are not recommended to be used in children due to the inability to precisely control the delivered drug dose and potential microbiological contamination (35). Young children are generally not cooperative to the use of nasal drops, and they often need to be restrained in the right position during the medicine administration. Nasal sprays are usually supplied in multidose containers with atomizing devices, or in pressured containers fitted with a suitable adapter, with or without a metering dose valve. The size of generated droplets, and the resulting spray pattern are such that spray deposition is localized in the nasal cavity (37). Sprays are easier to use, and therefore favourable to use in the paediatric population. Semi-solid nasal preparations are supplied in containers designed to deliver the product to the site of application (37).

Details on some example nasal formulations used in paediatric ARIs, their containers and administration/dosing devices are given in Table II.

Table II Examples of nasal preparations/dosage forms for drugs used in paediatric ARIs (6, 20-22)

Tabela II Primeri preparata/farmaceutskih oblika lekova za nazalnu upotrebu koji se primenjuju kod akutnih respiratornih infekcija u pedijatrijskoj populaciji (6, 20-22)

Active ingredient (content)	Dosage form and excipients	Therapeutic indications	Container
Oxymetazoline hydrochloride (0.025%)	i. Nasal drops, solution * ii. Nasal spray, solution* Excipients: Benzalkonium chloride; sodium hydroxide; sodium dihydrogen phosphate dihydrate; disodium phosphate dihydrate; water for injections	Used for the fast relief of symptoms of nasal congestion in cold, allergic rhinitis and rhinosinusitis; for children from 6 to 12 years	i. Dropper container ii. Bottle with a nasal spray pump
Xylometazoline hydrochloride (0.5 mg/ml)	i. Nasal drops, solution* ii. Nasal spray, solution* Excipients: Benzalkonium chloride, solution; disodium edetate; disodium phosphate dihydrate; sodium dihydrogen phosphate dihydrate; sodium chloride; sorbitol 70%, non-crystallizing; water, purified	Used for the relief of symptoms of nasal congestion, chronic and allergic rhinitis (including hay fever) and sinusitis; for children from 6 to 12 years	i. Dropper container ii. Bottle with a nasal spray pump
Naphazoline hydrochloride (0.05%)	Nasal drops, solution* Excipients: Boric acid; chlorobutanol, anhydrous; water for injections	Used for fast relief of nasal congestion in rhinitis and rhinosinusitis; for children from 7 years	Dropper container
Beclometasone dipropionate (50 µg/dose)	Nasal drops, suspension* Excipients: Avicel RC 591; glucose, anhydrous; benzalkonium chloride; phenylethyl alcohol; polysorbate 80; hydrochloric acid, dilute; purified water	Used in prophylaxis and treatment of perennial and seasonal allergic rhinitis including hay fever, and vasomotor rhinitis; for children from 6 years	Bottle fitted with a metering atomising pump

* registered in the Republic of Serbia

Preparations for inhalation

Inhaled medicines are often used in children with ARIs, although the use of certain inhaled drugs is not always justified (e.g., the use of corticosteroids in some ARIs) (40). Some examples of the inhalation medicines used in paediatric ARIs are listed in Table III. In general, inhalation drug delivery offers a lot of advantages: delivery of drugs to the site of action, faster therapeutic onset, reduced drug doses to achieve therapeutic effect

and lesser side effects. However, none of these benefits is achieved if the choice of inhaler and inhalation technique are not adequate.

The choice of inhaler depends upon a child's age and condition, but also upon the compliance regarding the adequate usage of an inhalation device. Nebulizers are suitable for young children and children with severe airway obstruction, because they do not require coordination between respiration and aerosol delivery. They should be used in combination with a face mask. Beside commercial drugs, hypertonic saline may also be administered by nebulization to infants to decrease airway edema and improve mucociliary clearance in certain ARIs conditions (40). Pressurized metered-dose inhalers (pMDIs) come as multidose preparations, and their major advantage is that they are compact and thus easily portable. Some commercial devices are breath-coordinated or breath-actuated and therefore suitable for children (41). pMDIs can be used with a spacer, or a combination of a spacer and face mask, e.g. in infants (because they are nose breathers) or severely ill children. Inhalation hood may also serve as an alternative for a face mask in very young children, as demonstrated in a study on infants suffering from viral bronchiolitis (42). Dry powder inhalers (DPIs) are another type of inhalers, which are compact and relatively easy to use, but they are only suitable for older children (with sufficient inspiration flow rate).

In relation to the inhaler type, inhalation technique is also an important factor that influences the efficacy of inhaled medicines. The paediatric population is especially susceptible to the issues of low compliance and/or inadequate inhalation technique, and therefore good interaction with the patient and timely training (of both parents/caregivers and pediatric patients) are of utmost importance to achieve the desired therapeutic goal.

Table III Examples of inhalation preparations used in paediatric ARIs (6, 20-22)

Tabela III Primeri inhalacionih preparata koji se primenjuju kod akutnih respiratornih infekcija u pedijatrijskoj populaciji (6, 20-22)

Active ingredient (content)	Dosage form and excipients	Therapeutic indications	Notes
Ipratropium bromide (i. 20 µg/dose) (ii. 500 µg/2 ml)	i. MDI ii. Nebuliser solution* Excipients: i. HFA-134a; ethanol anhydrous; purified water; citric acid anhydrous ii. Sodium chloride; water for injection; hydrochloric acid	Indicated for e.g., bronchitis, bronchospasm, blocked nose, rhinorrhea, cold, rhinitis, hayfever	For children from 6 years; in younger children only for the treatment of acute asthma
Beclometasone dipropionate (250 µg/dose)	MDI** Excipients: HFA-134a; ethanol anhydrous; glycerol	Exhibits an anti-inflammatory effect within the respiratory tract	For children from 4 years

Active ingredient (content)	Dosage form and excipients	Therapeutic indications	Notes
Budesonide (i. 200 µg/dose, 400 µg/dose) (ii. 0.25 mg/ml, 0.5 mg/ml)	i. DPI** ii. Nebuliser suspension** Excipients: i. Lactose monohydrate ii. Disodium edetate; sodium chloride; polysorbate 80; citric acid; sodium citrate; water for injection	Indicated for croup in infants and toddlers; also used in children with bronchopulmonary dysplasia with spontaneous respiration	i. For children from 5 years ii. For children from 3 months
Tobramycin (i. 28 mg/dose) (ii. 300 mg/4 ml)	i. DPI** ii. Nebuliser solution** Excipients: i. 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); calcium chloride; sulfuric acid ii. Sodium chloride; sulphuric acid; sodium hydroxide; water for injection	Indicated for pulmonary infections caused by <i>Pseudomonas aeruginosa</i> in patients with cystic fibrosis	For children from 6 years
Zanamivir (5 mg/dose)	DPI** Excipients: Lactose monohydrate	Indicated for treatment of influenza A and B	For children from 5 years
Acetylcysteine (i. 300 mg/3 ml) (ii. 100 mg/ml; 200 mg/ml)	i. Solution for injection** ii. Solution for inhalation Excipients: i. Disodium edetate; sodium hydroxide; water for injection ii. Disodium edetate; water for injection	Used as a mucolytic adjuvant in the therapy of respiratory disorders such as bronchitis, emphysema, mucoviscidosis, bronchiectasis	i. The solution can be administered via inhalation (recommended by pressurized inhalers); for children from 2 years ii. The 20% solution may be diluted to a lesser concentration; the 10% solution may be used undiluted; should be administered via nebulization using a face mask, mouth piece or inhalation hood; doses are given in relation to body weight (age groups are not specified)

* registered in the Republic of Serbia (import license); ** registered in the Republic of Serbia

Extemporaneous compounding

Compounding pharmacies have an important role in paediatric medicine, since they can offer solutions to unique patient needs (43). A compounding pharmacist must have access to compounding resources of adequate quality (both active and inactive pharmaceutical substances), while using professional knowledge and skills to prepare formulations/dosage forms that meet the specific needs of paediatric patients (30).

Medication can be tailored to the child to allow better compliance in cases when commercial medicines are not available in adequate strength, an appropriate drug dosage form is not available, the active substance or commercial medicine has inadequate organoleptic properties, or a medicine is not available from suppliers, e.g., due to shortages (43, 44). However, pharmaceutical compounding is associated with certain risks, such as potential errors in dose calculation, replacement of the drug substance with another one of similar name, inappropriate choice of excipients (leading to, e.g.,

incompatibilities, inadequate acceptability in terms of a medicine taste or color in relation to the patient's age), errors during compounding (e.g., weighing or preparation), inadequate selection of packaging and/or measuring/dose devices which can lead to inaccuracy in dosing, stability issues (chemical, physical or microbiological), unknown bioavailability, efficacy and/or safety (due to a lack of data from relevant studies) or the occurrence of adverse drug reactions (45-47). Consequently, there are concerns related to the quality control and safety of medicinal products compounded in pharmacies, which is a widespread practice in European countries (48).

In this context, recommendations from legislation and professional literature related to the subject are of great importance in ensuring the quality of a compounded medicinal products. For example, the United States Pharmacopeia (49) provides general information to enhance the pharmacist's ability in compounding and validate procedures and requirements (50). In Europe, in addition to national guidelines and recommendations, the most important step toward this aim was the adoption of a *Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients* by the Committee of Ministers of the Council of Europe in 2011 (the current effective version of the document is Resolution CM/Res (2016)1 (51). This document recognizes the need to provide personalized/individualized therapy to certain categories of patients. Therefore, it aims to harmonize quality and safety assurance and standards for medicinal products prepared in pharmacy and to fill the gap in quality and safety assurance between these preparations and medicinal products produced by the pharmaceutical industry (50, 51). The Resolution recommends that all compounded medicinal products should be prepared using an appropriate quality assurance system. Risk assessment should always be carried out prior to a product preparation, in order to define the level of the quality assurance system which should be applied during the preparation of the medicinal product. The Resolution states that two risk levels of a compounded medicinal product can be distinguished (i.e., "high-risk preparations" and "low-risk preparations"), as well as two different levels of the quality assurance system (i.e., GMP guide recommended for "high-risk preparations", and the PIC/S Good Preparation Practices Guide (52) for "low-risk preparations") (51). An example of a high-risk preparation is *Gentamicin 40 mg/ml for Inhalation* (53). All of the above also applies to pharmacy-prepared medicines for children.

Conventional pharmaceutical dosage forms, such as liquid preparations for oral use (e.g., oral solutions, oral suspensions, oral emulsions), solid oral preparation (e.g., divided powders or sprinkle formulations) and preparations for cutaneous application (e.g., gels, creams, ointments) are the most frequently compounded products in pharmacies for individual needs of paediatric patients. However, the introduction of modern excipients and improvements in compounding procedures, along with appropriate pharmacists' knowledge and continuous training, have led to the design of novel dosage forms such as lollipops, "gummies"/chewing lozenges, soft lozenges, orodispersible films or 3D printed paediatric solid dosage forms. Such a trend, although not equally present in all European

countries, is expected to improve children's compliance with medicines, including the medicines indicated in ARIs.

Conclusion

The overview of the utility of different dosage forms in children with ARIs indicates a general lack of age-appropriate formulations. As a consequence, the prevalence of off-label and unlicensed medicine use is still high in all paediatric age groups. Regulatory authorities and professional groups have issued recommendations on the selection of age-appropriate excipients and dosage forms for children. Moreover, *ex tempore* compounding may also fit the needs for personalized therapy in the paediatric population. In line with these facts and recommendations, future efforts are expected to provide more effective and safe pharmacotherapy in children with ARIs.

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Stavovi i saveti vezani za izbor farmaceutskih oblika lekova za lečenje respiratornih infekcija kod dece

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Kratak sadržaj

Terapija respiratornih infekcija kod dece zahteva posebnu pažnju, jer ovu populaciju čini specifična i izuzetno heterogena grupa pacijenata. Veoma je važno odabrati odgovarajući farmaceutski oblik leka, u skladu sa karakteristikama aktivne supstance, kao i stanjem i uzrastom deteta. U praksi se, u terapiji respiratornih infekcija kod dece, najviše koriste preparati za oralnu primenu, za parenteralnu primenu i za inhalaciju. Međutim, veliki broj lekova nije dostupan u odgovarajućem farmaceutskom obliku i/ili jačini za pedijatrijski uzrast, usled čega je česta neodobrena upotreba lekova. Prilikom izbora/izrada preparata za decu potrebno je pažljivo razmotriti i sastav preparata (bezbednost pomoćnih supstanci), kao i izbor aplikatora, u skladu sa uzrastom deteta.

U ovom radu je dat prikaz farmaceutskih oblika lekova koji se koriste u terapiji respiratornih infekcija kod dece, njihovih prednosti i izvesnih nedostataka. Navedeni su različiti primeri farmaceutskih preparata, uz poseban osvrt na izbor aplikatora za primenu/doziranje lekova. Takođe, diskutovane su specifičnosti pedijatrijske populacije koje utiču na izbor odgovarajuće formulacije leka prilagođene uzrastu deteta.

Ključne reči: farmaceutski oblici lekova za decu,
lekovi prilagođeni pedijatrijskom uzrastu,
izrada magistralnih lekova,
aplikatori za primenu/doziranje lekova, respiratorne infekcije
