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Delivery of inhalation drugs to children for asthma and other respiratory diseases

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Abstract

Infants and children constitute a patient group that have unique requirements in pulmonary drug delivery. Since their lungs develop continuously until they reach adulthood, the airways undergo changes in dimensions and number. Computational models have been devised on the growth dynamics of the airways during childhood, as well as the particle deposition mechanisms in these growing lungs. The models indicate that total aerosol deposition in the body decreases with age, while deposition in the lungs increases with age. This has been observed on paediatric subjects in *in vivo* studies. Issues unique to children in pulmonary drug delivery include their lower tidal volume, highly variable breathing patterns, air leaks from facemasks, and the off-label or unlicensed use of pharmaceutical products due to lack of clinical data for this age group. The aerosol devices used are essentially those developed for adult patients that have been adapted to paediatric use. Facemasks should be used with nebulisers and spacers for infants and young children. An idealised throat that mimic the average particle deposition in paediatric throats have been designed to obtain more clinically relevant aerosol dispersion data *in vitro*. More effort should be spent on studying particle deposition in the paediatric lung and developing products specific for this subpopulation to meet their needs.

Introduction

'Children are not just small adults' is a popular cliché [1]. Indeed, much of their anatomy and physiology undergo development before adulthood so paediatric patients have unique requirements in drug delivery that differ from those of adults. For pulmonary drug delivery, these are mainly due to the smaller geometry of the respiratory tract and the lower inhalation flow rates. These fundamental characteristics consequently affect particle deposition in the airways and the performance of pharmaceutical inhalers. This review explores these aspects of paediatric inhaled drug delivery.

Age classification of paediatric patients

The upper age limit of paediatric patients differs depending on the regulatory authority. Since growth is a major trait of childhood, this patient group is heterogeneous and may be subdivided according to age or physiological maturity. Table 1 shows the age classifications from the United States of America Food and Drug Administration (FDA) [2], the European Agency for the Evaluation of Medicinal Products (EMEA) [3], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [4], and the World Health Organisation (WHO) [5]. Although the naming and age bands of the categories between the regulatory authorities are slightly different, the broad divisions are similar, namely, (a) 0 – 1 month, (b) 1 month – 2 years, (c) 2 – 12 years, and (d) 12 – 16 to 21 years. The WHO classification is more comprehensive as it distinguishes between the young child (2 – 6 years) from the child (6 – 12 years) as well as including categories for premature and term newborns. Since its upper age limit of 18 years old is

covered by the other regulatory classifications and is the most common minimum voting age throughout the world [6], the WHO classification will be followed in this review article.

Particle deposition in the respiratory tract

Theory of particle deposition in the airways

The major particle deposition mechanisms in the respiratory tract are inertial impaction, sedimentation, and diffusion [7]. These are governed by the following relationships [8]:

$$\text{Deposition by impaction} \propto \frac{\rho d^2 Q}{D^3} \quad \text{(Equation 1)}$$

$$\text{Deposition by sedimentation} \propto \frac{\rho d^2 DL}{Q} \quad \text{(Equation 2)}$$

$$\text{Deposition by diffusion} \propto \frac{L}{Qd} \quad \text{(Equation 3)}$$

where ρ is the particle density, d the particle diameter, D the airway diameter, L the length of the airway section, and Q the airflow rate. The equations above show that deposition is affected by dimensions of the airway, besides particle size and density. This is of particular significance for paediatric patients because firstly, their airways are smaller than those of adults. Therefore, particle deposition in the lungs in children is different to that in adults. Secondly, since paediatric airways undergo substantial growth before adulthood, particle deposition change with age during this period [8]. From the equations, airway dimensions (D and L) affect impaction, sedimentation, and diffusion in decreasing order of influence. This is because D is a cubic variable in Equation 1 so its effect is the greatest. On the other hand, the product DL in Equation 2 can be considered as a quadratic variable of airway dimensions and

L is a linear variable in Equation 3 so their power is less stepwise. It can be deduced that particle deposition by impaction is higher in children than in adults due to the smaller *D*. Besides having smaller airways, children also have lower respiratory flow rates [8]. The equations show that airflow rate (*Q*) has the opposite effect to airway dimensions on deposition. However, since *Q* is a linear variable, its effect is less than that of *D* and *L* in Equations 1 and 2. Therefore, the overall influence of the smaller airways in children overpowers that of the lower airflow rate [8]. This is reflected in the increase in total particle deposition with a decrease in age (see below).

Computational deposition models

Knowledge on the theoretical particle deposition in children was primarily derived from mathematical modelling in the 1980s and 1990s [9-13]. With the advancement of computer technology in later decades, computational fluid dynamics (CFD) was employed to examine the airflow pattern inside the airways [14-17]. However, research on deposition modelling in paediatric airways is less than that in adults overall.

Hofmann [9] proposed a mathematical model for delineating the growth of the lung as a function of age. The calculation was based on the Weibel dichotomous airway model A fitted with morphometric data of various airway parameters at different ages. The pulmonary parameters included the dimensions of the trachea, main bronchi, terminal bronchioles, and alveoli; the number of respiratory airways and alveoli; and the total lung volume [9]. In accordance to morphometric observations, the lungs undergo two phases of growth in this model. From birth to about eight years old, new respiratory airways and the linings of these

with the alveoli form. Beyond eight years, the pulmonary structure is completed and further growth results from increases in the linear dimensions of the airways [9].

Xu and Yu [10] investigated the total and regional deposition of orally inhaled particles (0.01–10 μm) in their lung model for 0 to 30-year olds with tidal breathing. Regional deposition was deposition in the head, tracheobronchi, and alveoli. It was found that the trend of total and regional deposition with respect to particle size was similar across the ages [10]. However, the total deposition in children was higher than that in adults for all particle sizes. Deposition in the head was higher in children for particles 5 μm and larger in size. On the other hand, deposition in the tracheobronchial and alveolar regions showed no clear dependency with age or particle size [10]. The head region is essentially the oropharynx, where large particles (> 5 μm) deposit by inertial impaction [7]. Since airway diameter is a cubic variable for impaction (Equation 1), deposition by this mechanism is expected to be significantly higher in children, whose throats are smaller [8]. This is supported by the finding from Xu and Yu [10].

An increase in the total deposition in children was also observed in another model [13]. This study utilised purely algebraic calculations rather than a branched airway model and only considered the inspiration phase. Total deposition was considered as filtration efficiency, η, which was expressed as

$$\eta = (0.12 - 0.002Y + \frac{0.5}{Y}) d^{1.1} V_t^{0.33} T^{0.54} \quad \text{(Equation 4)}$$

where Y is the age in years, d the particle aerodynamic diameter, V_T the tidal volume, and T the breathing period. The calculated total deposition (i.e. filtration efficiency) agreed well

with experimental data from the inhalation of monodisperse polystyrene particles by healthy human subjects between 5–25 years old [13]. If d, V_T, and T are kept constant in Equation 4, then by substituting Y with actual ages, the total deposition in a 5-year old is 2.3 times that in a 25-year old. Filtration efficiencies for the tracheobronchial (η_{TB}) and alveolar regions (η_A) were also derived but experimental data were not available for their verification.

$$\eta_{TB} = 0.06d^{1.34} \quad \text{when } T \leq T_0 \quad \text{(Equation 5)}$$

$$\eta_{TB} = 0.06d^{1.34}T^{0.3} \quad \text{when } T > T_0 \quad \text{(Equation 6)}$$

$$\eta_A = (0.11 - 0.0027Y)d^{0.93}V_t^{0.51}T^{0.72} \quad \text{(Equation 7)}$$

where T_0 was the standard breathing period of a given age at tidal breathing used as a point of reference for the actual breathing period T [13]. These equations show that while alveolar deposition was dependent on all the variables considered, tracheobronchial deposition was independent of age and tidal volume. On the contrary, Phalen et al found that tracheobronchial deposition decreased with age from 2–18 years old using mathematical models derived from paediatric lung casts [11]. This trend was observed across various particle sizes (0.05–10 μm) and breathing airflow rates at low activity and low exertion. The tracheobronchial dose per kilogram of body mass for 5 μm particles was six-fold lower in a resting adult than in a resting newborn. At high exertion, tracheobronchial deposition decreased with age for particles < 0.5 μm but increased with age for larger particles [11]. The predicted tracheobronchial deposition profiles from Phalen et al [11] under low activity conditions agreed well with those from Hofmann et al [12], even though the latter study used different equations in the calculations, considered the complete inspiratory-expiratory cycle,

and included both tracheobronchial and alveolar (termed 'pulmonary' in [12]) deposition. The model by Hofmann et al [12] was thus more comprehensive. It showed that under sedentary activity, tracheobronchial deposition decreased with age (7 months to adult) and alveolar deposition increased with age across all particle sizes (0.01–10 μm). However, the total deposition (the sum of tracheobronchial and alveolar deposition) showed no clear age-dependency [12]. Total and regional deposition under maximal activity (i.e. fast respiratory rate) also showed complex trends [12]. It is interesting to note that the increase in alveolar deposition with age under sedentary activity supports the direct proportional relationship between η_A and Y in Equation 7.

The effect of constricted airways, such as those during an asthma attack, in a paediatric CFD lung model on particle transport and deposition was investigated by Longest et al [16]. Upper and central airway models were constructed for a four-year old child, one set with normal airway dimensions and another with a 30% reduction in airway diameter [16]. The airflow rates used for the modelling were the same as those for sedentary, light activity, and heavy activity conditions reported in Hofmann et al [12]. It was found that airway constriction significantly increased the deposition of 1–7 μm particles at airway branches and at the local cellular-level for all three airflow rates. This implies that drug delivery to the lungs or pulmonary exposure to inhaled environmental particles could be different during an asthma attack.

In vivo *deposition studies*

Although there are differences between the results of the deposition modelling studies discussed in the previous section, the general consensus is that total deposition in the

respiratory tract is higher in younger children. However, deposition in the deeper airways would be lower in paediatric subjects because oropharyngeal deposition is more significant. This consequently reduces the amount of particles that travel further downstream [8]. The higher total and oropharyngeal deposition [18-20], as well as lower lung deposition [19-24], in younger children have been observed in *in vivo* studies. The higher total and oropharyngeal deposition for particles ≥ 5 μm was predicted by the paediatric model by Xu and Yu discussed above [10], whereas the lower lung deposition with age is in line with the model by Phalen et al [11]. However, no single paediatric model so far can accurately predict the total and regional depositions. The findings derived from some models do not even agree with each other. This is because there is limited anatomical and physiological data of the young airways. In addition, *in vivo* deposition data on paediatric subjects are limited for verifying the models.

A number of *in vivo* deposition measurements conducted on children included direct scintigraphic imaging studies using radiolabelled aerosols [19-22, 25-30] and indirect studies using calculated deposition [18, 31] or pharmacokinetic/pharmacodynamic assessments [31-33]. It is clear from these studies that nebulised droplets and particles produced from metered dose inhalers (MDIs) can deposit in the paediatric airways *in vivo*. However, the proportion of drug that reaches the lungs is generally low. The mean lung dose of technetium-99m-labelled radiolabelled aerosols given by jet nebulisers and suspension MDIs with spacers was typically 5% of the administered dose or lower [21, 22, 25, 26, 28, 33, 34]. The mode of breathing was tidal through facemasks in these studies. Filtration of particles by the nasal cavity has been suggested as a major cause of the low deposition in the lungs [33]. The low tidal volume in children may have also decreased the aerosol inhaled (see next section).

Another factor for the low lung doses in the studies mentioned above was the large droplet or particle sizes employed, which were > 3 μm. Higher lung deposition could be achieved when the particle size was reduced. This was seen in children who used the hydrofluoroalkane (HFA) MDI solution formulation of beclomethasone dipropionate (QVAR™). This product produces droplets with a mass median aerodynamic diameter (MMAD) of 1.1 μm so deposition in the peripheral airways should be high [19]. Indeed, the mean lung dose of the QVAR™ Autohaler, a breath-actuated MDI used without a spacer, ranged from 36.9–54.1% of the ex-actuator dose in children aged 5–14 years. Even higher lung doses could be achieved when a conventional QVAR™ MDI coupled to an Aerochamber Plus™ spacer was used with a slow maximal inhalation followed by a 5–10 s breath-hold [20]. The mean lung dose ranged from 56.6–58.4% of the ex-actuator dose in children aged 5–17 years [20]. In contrast, the same device configuration used with tidal breathing yielded mean lung doses of 35.4, 47.5, and 54.9% for subjects aged 5–7, 8–10, and 11–17 years, respectively [20]. The breath-holding manoeuver thus eliminated the age-dependency of the lung dose. It also reduced oropharyngeal and gastrointesintal drug deposition [20].

Special requirements in paediatric respiratory drug delivery

There are generic requirements for delivering pharmaceutical aerosols to both children and adults, namely, optimal particle size range (1–5 μm aerodynamic diameter), minimal oropharyngeal deposition, and simple, affordable, and reliable aerosol devices [24]. However, paediatric patients also have special needs that are absent, or are not as significant, in adults. The lower tidal volume of children obviously reduces dose delivery [24]. Infants and children also have highly variable breathing patterns. Their inspiratory flow rates range from nearly 0 to about 40 L/min [24]. Moreover, infants cannot adopt any stipulated breathing patterns so

they can only breathe tidally through the nose [35]. Thus they must need facemasks for aerosol administration. Children of two and a half to three years old would have sufficient ability to use a mouthpiece [35]. However, if the infant or child is emotionally upset and cries, then drug delivery will be adversely affected. The breathing pattern will change and the inspiratory flow rate will increase, which leads to higher deposition in the proximal airways [24, 35]. The facemask seal will also loosen when child is upset and cause aerosol leakage [35]. The problems discussed above need to be considered when designing, testing, and using pharmaceutical aerosol products to optimise delivery in children.

Another issue with paediatric drug delivery, not unique to the inhalation route, is the unlicensed or off-label use of marketed products in infants and young children [36, 37]. Unlicensed use is the use of a product that is not approved in a particular age group (or in humans) [37]. Off-label use is the use of a product approved for the given age group but it is used in an unapproved manner or dosage regimen [37]. Most pharmaceutical products were approved from clinical studies in adults or older children (≥ 6 years old) [36]. Pharmaceutical companies have little incentives to conduct trials on younger subjects due to the complexity and high cost. Therefore, paediatricians are faced with the difficulty of choosing the appropriate drug, dosage, and device because there is a lack of clinical data that can serve as a guide [36]. Nevertheless, unlicensed and off-label uses of inhalation products are very common [37], especially in infants and children < 6 years old [36]. The gap in drug use knowledge in this age group is an unmet need that needs to be addressed. Collaborative research and sharing of data between academic and industrial researchers may assist regulators and prescribers in improving and standardising drug use in young paediatric patients [36].

Pharmaceutical aerosol devices

Nebulisers

Nebulisers had been the most commonly used aerosol device in children because the patient can inhale the droplets at a natural pace, without the need for coordination. The jet nebuliser is the oldest type that uses a compressed gas to atomise the liquid. The gas is usually air that is pumped by an electrical air compressor. Treatment times are long, ranging from 5–15 minutes. It is also bulky so it is usually used at home or in the hospital. Their droplet size and drug output are dependent on the model of the nebuliser and the breathing pattern [38-40]. Ultrasonic nebulisers are smaller than jet nebulisers and produce droplets by the application of ultrasonic waves through the liquid from a piezoelectric element at the bottom of the reservoir. However, the energy input heats up the liquid so they are not suitable for protein drugs. The newest type of nebuliser is the vibrating mesh nebuliser. When in operation, a mesh with small laser-drilled holes rapidly vibrates against the surface of the liquid and eject out the droplets. The vibrating mesh nebuliser has shorter treatment times and lower residual volumes (i.e. less liquid wastage) than jet and ultrasonic nebulisers.

It has long been demonstrated that delivering drugs using a MDI with a spacer can achieve the same therapeutic outcomes as that using a nebuliser [24]. This changeover is practical as long as the drug of interest is available in both MDI and nebule forms. Comparisons between MDIs and nebulisers are discussed in the next section.

Metered dose inhalers and spacers

To use MDIs properly, the patient needs to coordinate actuation and inhalation. This is difficult for children thus spacers are used as an accessory to hold the aerosol while the child breathes tidally. The one-way inhalation valve inside the spacer must have low resistance so that it opens readily at low airflow rates. Besides eliminating the need for coordination, it provides space and time for the propellant droplets to evaporate and decelerate, reducing the particle size. This in turn decreases oropharyngeal deposition and potential systemic absorption through the gastrointestinal tract. Discomfort from the 'cold Freon' effect, which is due to the flash evaporation of the propellant, is also avoided. The volume of the spacer is important because if it is much larger than the tidal volume then the dose will not be sufficiently inhaled by the patient. Tidal volumes range from 75 mL for a 6-month old child, to 325 mL for an 8-year old, and to 750 for an adult male [8]. Typical spacer volumes range from 200–500 mL. The large spacers should not be used on infants or children with small tidal volumes.

There are various commercially available spacers with different dimensions, geometries, volumes, and designs. These differences, together with the MDI formulation and tidal breathing pattern, can affect the fine particle dose delivered [41]. Using replicas of infant (7 month old) and child (4 years old) faces, particles produced from Ventolin® and Beclovent® MDIs through a Space-Chamber® spacer were collected through the simulated nostrils and into an Andersen Mark II cascade impactor while tidal breathing occurred through the spacer [42]. It was found that less drug was collected with the infant face replica than the child replica. This is analogous to the lower total deposition in younger subjects discussed above. The difference was due to more large particles being collected with the child replica. The amount of fine particles < 2.1 μm for Ventolin® and < 3.3 μm for Beclovent® was not affected by the face replicas [42].

The usefulness of spacers has been demonstrated in many studies. Asthmatic children (mean age = 6 years) who used MDIs with spacer showed earlier resolution of wheezing, fewer days of cough after an asthma attack, and shorter absence from school after an asthma attack compared to those who used MDIs alone [43]. In studies that compared the MDIs plus spacer to nebulised therapy, the former treatment was always demonstrated to be as effective as, or better than, the latter [22, 32, 44, 45]. Supported by these findings, patients are encouraged to use MDIs and spacers instead of nebulisers, especially because the former are more portable and easier to use.

Facemasks

Facemasks are interface accessories commonly used with nebulisers and spacers for infants and young children. It is important that the facemask establishes a tight seal on the child's face because even a small leak can significantly decrease aerosol delivery efficiency. This effect has been shown in an *in vivo* study on wheezy children (18–36 months old) [46]. When they inhaled radiolabelled salbutamol from a MDI plus a spacer, the lung deposition with respect to the metered dose was 0.2% in children who inhaled from a loosely fitted facemask, 0.6% in screaming children with a tightly fitted facemask, and 4.8% in those who breathed normally [46]. The corresponding figures for nebulised radiolabelled salbutamol in those children were slightly higher but the trend was similar. These data indicate that not only the tightness of the facemask is crucial; the mode of breathing also greatly affects drug delivery. Indeed, an *in vitro* study using a breathing simulator and a paediatric face model with an inhaled mass filter connected to the simulated mouth, a crying breathing pattern reduced the inhaled drug mass to < 1% of the labelled dose for both nebulisers and MDI plus spacers [47].

Crying and screaming are real problems in uncooperative or upset children so approaches that minimise the distress must be developed to encourage tidal breathing [35].

Besides ensuring good aerosol delivery, the seal and shape of the facemask also affects facial and ocular deposition of the drug, which should be minimised [48, 49]. The design of the facemask such as minimal dead space, shape that fits snuggly to the contours of the face, and flexible construction material should be considered during product development. Two excellent and comprehensive reviews have been published on these aspects [50, 51]. However, even a facemask with the best design will fail if a child is uncooperative. The carer may keep the child calm with some games or distractions during aerosol administration [35].

Dry powder inhalers

Dry powder inhalers (DPIs) are passive devices that require the user's inspiratory effort to disperse the powder for inhalation. They are not recommended for children < 4 years old because younger ones cannot generate sufficiently high airflow through the devices [24, 36]. *In vivo* deposition of radiolabelled budesonide particles from a Turbuhaler® was tested on 3 to 16-year old cystic fibrosis subjects with normal lung function [30]. The lung dose was positively correlated with age and peak inspiratory flow. This is understandable because Turbuhaler® has relatively high airflow resistance so its performance is flow-dependent. Interestingly, after the lung dose was normalised against body weight for subjects > 6 years old there was no correlation with age [30]. This implies that although younger children inhaled lower lung doses due to the lower peak flows, the situation was counter-balanced by their lower body weights. Budesonide delivered from the Turbuhaler® has been shown to be more effective in 5 to 15-year old asthmatic patients than the same drug administered from a

MDI with a Nebuhaler spacer [52]. This was reflected in the lower usage of a bronchodilator (i.e. lower asthma attack incidence) in patients who used the Turbuhaler®, as well as no deterioration in asthma control when the Turbuhaler® budesonide dose was halved [52].

Unlike the Turbuhaler®, the aerosol performance of the Diskus™ inhaler is independent of airflow rate *in vitro* and *in vivo* [53]. Ninety-nine per cent of children from 3–10 years old could generate a flow rate of 30 L/min through the inhaler. On the other hand, 26% could achieve 90 L/min [53]. Fifty micrograms of salmeterol was inhaled by children aged 8–15 years at 30 or 90 L/min. The protective effect of the drug against bronchoconstriction was not significantly different between the two flow rates [53].

Soft Mist™ inhaler

The Respimat® Soft Mist™ inhaler (SMI) is a multidose inhaler that produces a fine mist from forcing a metered volume of aqueous drug solution through a set of fine channels in the nozzle [54]. It does not contain propellants. Rather, the atomisation energy comes from a tensioned spring inside the inhaler. The relatively long atomisation time (about 1.2 s) renders the mist slow-moving, hence reduces oropharyngeal deposition compared to MDIs [54]. A clinical study had been conducted on asthmatic patients aged 6–15 years to compare the efficacy of the combination treatment with ipratropium bromide and fenoterol hydrobromide delivered from the SMI and that from a MDI with spacer [54]. It was found that the drugs administered using the SMI was at least as effective, and was a safe as, that with the MDI and spacer [54].

Paediatric idealised throat

Aerosol performance is usually assessed *in vitro* by sampling the particles using a cascade impactor. From the amount of drug deposited on the impactor stages, the fine particle dose < 5 μm can be obtained as an indicator of the potentially inhalable dose. As mentioned above, the lung dose is greatly affected by deposition in the nasal and oropharyngeal region. The conventional United States Pharmacopeia induction port for *in vitro* impaction experiments constitutes a 90° bend. This design is too simple to faithfully simulate particle deposition in a human throat, whether for adults or children. Thus it is important to use an aerosol induction port that yields clinically relevant particle deposition. Anatomical replicas of the paediatric nasal cavity and upper airways have been constructed from three-dimensional computed tomography (CT) or magnetic resonance imaging (MRI) scans of infants and children [55-61]. Their usefulness in replicating paediatric throat deposition has been demonstrated *in vitro*. However, each anatomical replica is different so there is a need to design a simplified throat model that can provide representative deposition data to standardise usage with impactors. The commercially available Alberta Idealised Throat is such a model developed from CT scans of adult throats and subsequent simplification [62]. A downscaled version of this throat successfully replicated the average paediatric oropharyngeal deposition in throat replicas of 6 to 14-year olds [63]. A similar paediatric idealised throat representing the upper airway of a 4 to 5–year old has recently been used to assess the performance of two dry powder inhalers on a Next Generation Impactor (NGI) [64].

Conclusion

Paediatric patients constitute a subpopulation with special needs for pulmonary drug delivery. More knowledge is needed on the anatomical and physiological changes in their lungs during growth. Academic and industrial researchers should devote more efforts in paediatric drug delivery. This will facilitate the design and use of pharmaceutical aerosol products to suit this special patient group.

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Table 1. Age classifications of paediatric patients from the FDA [2], EMA [3], ICH [4], and WHO [5].

FDA	
Neonates	0 – 28 days
Infants	29 days – Less than 2 years
Children	2 years – Less than 12 years
Adolescents	12 years – 21 years (up to, but not including the 22nd birthday)
EMA and ICH	
Preterm newborn infants	
Term newborn infants	0 – 27 days
Infants and toddlers	28 days – 23 months
Children	2 – 11 years
Adolescents	12 – 16 to 18 years depending on the region
WHO	
Premature newborns	< 38 weeks gestational age
Term newborns	> 38 weeks gestational age
Neonate	0 – 30 days
Infant	1 month – 2 years
Young child	2 – 6 years
Child	6 – 12 years
Adolescent	12 – 18 years