

**EFFECTIVENESS OF PHARMACIST-LED  
EDUCATIONAL INTERVENTIONS ON  
PRACTICES OF ORAL ANTIBIOTIC  
SUSPENSIONS RECONSTITUTIONS, DOSAGE  
MEASUREMENT AND STORAGE AMONG  
PARENTS IN RURAL AREA, KEDAH**

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**UNIVERSITI SAINS MALAYSIA**

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by

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## LIST OF ABBREVIATIONS

BMI	Body Mass Index
BSA	Bosy Surface Area
IBW	Ideal Body Weight
LDT	Low Dose Tip
NCMS	Malaysian National Medical Care Survey
PKPD	Pharmacokinetic-pharmacodynamic
TBW	Total Body Weight
URTI	Upper Respiratory Tract Infection
USM	Universiti Sains Malaysia

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**KEBERKESANAN INTERVENSI PENDIDIKAN OLEH AHLI FARMASI  
TERHADAP PRAKTIS REKONSTITUSI, PENYUKATAN DOS, DAN  
PENYIMPANAN UBAT ANTIBIOTIK DALAM KALANGAN IBU BAPA DI  
KAWASAN PEDALAMAN KEDAH**

**ABSTRAK**

Ubat antibiotik biasanya digunakan untuk rawatan jangkitan bakteria dalam kalangan pesakit kanak-kanak. Kajian terdahulu menunjukkan pelbagai masalah yang biasanya berkaitan dengan penggunaan antibiotik, rekonstitusi, dan penyimpanan ubat antibiotik dalam kalangan ibu bapa. Namun demikian, kajian yang dijalankan sebelum ini lebih tertumpu kepada intervensi untuk meningkatkan pengetahuan ibu bapa dalam rekonstitusi antibiotik daripada menerokai praktis rekonstitusi dan penyimpanan antibiotik. Kajian ini dijalankan di kawasan luar bandar, Kedah, Malaysia. Kajian ini bertujuan untuk menilai keberkesanan kaunseling ahli farmasi terhadap praktis ibu bapa dalam penggunaan antibiotik, rekonstitusi, penyimpanan dan penyukatan dos suspensi antibiotik. Fasa pertama kajian ini melibatkan reka cipta senarai semak kaunseling mengenai penggunaan antibiotik, rekonstitusi, penyimpanan dan pengukuran dos suspensi antibiotik. Selain itu, edaran rekonstitusi dan penyimpanan antibiotik juga direkacipta dalam kajian ini. Fasa kedua kajian ini melibatkan penilaian keberkesanan kaunseling ahli farmasi berpandukan senarai semak dan edaran yang direka cipta dalam fasa pertama kajian. Pengetahuan dan teknik ibu bapa dalam penggunaan antibiotik, rekonstitusi, penyimpanan dan penyukatan dos suspensi antibiotik telah dinilai sebelum dan selepas kaunseling ahli farmasi. Ibu bapa juga dikehendaki menunjukkan cara rekonstitusi suspensi antibiotik dan teknik penyukatan dos semasa sesi kaunseling dengan menggunakan kit demonstrasi yang disediakan.

Sejumlah 330 ibu bapa menyertai kajian ini. Praktis dan pengetahuan ibu bapa telah diberi markah penilaian sebelum dan selepas kaunseling ahli farmasi. Keputusan kajian ini menunjukkan bahawa jumlah ibu bapa yang mendapat markah penuh dalam penilaian pengetahuan mereka terhadap penggunaan antibiotik, rekonstitusi dan penyimpanan suspensi antibiotik telah meningkat sebanyak 33% selepas kaunseling ahli farmasi. Markah median ibu bapa dalam penggunaan antibiotik, rekonstitusi dan penyimpanan suspensi antibiotik (markah penuh = 34) telah meningkat dari 20 markah (IQR: 18 - 22) ke 33 markah (IQR: 32 - 34). Markah median ibu bapa dalam rekonstitusi antibiotik (markah penuh = 7) telah meningkat dengan ketara dari 3 markah (IQR: 2 - 4) ke 7 markah (IQR: 7). Peratusan ibu bapa yang mendapat markah penuh (markah penuh = 7) dalam penilaian teknik rekonstitusi dan pengukuran dos antibiotik telah meningkat dengan ketara dari 1.5% ke 78.5%. Kajian ini menunjukkan bahawa kaunseling ahli farmasi dengan bantuan edaran rekonstitusi dan penyimpanan suspensi antibiotik adalah berkesan untuk menambahbaik pengetahuan dan teknik ibu bapa dalam penggunaan antibiotik, rekonstitusi, penyimpanan dan penyukatan dos suspensi antibiotik. Edaran rekonstitusi dan penyimpanan suspensi antibiotik yang disediakan dalam kajian ini boleh digunakan dalam kerja harian ahli farmasi untuk pendispensan dan kaunseling suspensi antibiotik.

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INTERVENTIONS ON PRACTICES OF ORAL ANTIBIOTIC  
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STORAGE AMONG PARENTS IN RURAL AREA, KEDAH**

**ABSTRACT**

Antibiotic suspensions is commonly prescribed for paediatric patients for the treatment of bacterial infections. Previous studies have demonstrated the common problems associated with antibiotic use, reconstitutions, and storage among parents. Meanwhile some studies only focussed on the interventions to improve parent's knowledge on antibiotic reconstitutions rather than exploring the problems of parent's malpractice on antibiotic reconstitution and storage. This study was conducted in a rural area of Kedah, Malaysia. This study aimed to assess the effectiveness of pharmacist's counselling on the parents' practices of antibiotic use, antibiotic suspensions reconstitution, storage, and dose measurement. The first phase of the study involved the development of a counselling checklist on antibiotic use, reconstitution, storage and dose measurement. Besides, an antibiotic reconstitution and storage handout was developed. The second phase of the study involved the assessment of the effectiveness of the pharmacist's counselling guided by the checklist and handout developed in phase one study. The parent's knowledge and technique on antibiotic use, antibiotic suspensions reconstitution, storage, and dose measurement were assessed at pre and post pharmacist counselling. The parents were required to demonstrate the antibiotic suspensions reconstitution and dose measurement technique during the counselling session using a demonstration kit. There was a total of 330 parents

recruited into the study. The parents' practices and knowledge was scored before and after the pharmacist counselling. The results showed that the proportions of parents who scored perfectly on their knowledge on antibiotic use, reconstitution and storage has increased by 33% after the pharmacist counselling. The parent's median score on antibiotic use, reconstitution, and storage (perfect score = 34) has increased from 20 (IQR: 18 - 22) to 33 (IQR: 32 – 34). The average parent's median score on antibiotic reconstitution technique (perfect score = 7) has increased significantly from 3 (IQR: 2 - 4) to 7 (IQR: 7). The proportion of parents who scored perfectly (perfect score = 7) in the antibiotic suspension reconstitution and dose measurement technique assessment, has increased tremendously from 1.5% to 78.5%. This study showed that the pharmacist counselling with the help of antibiotic suspensions reconstitution and storage handout was effective in improving the parents' knowledge and technique on antibiotic use, antibiotic suspensions reconstitution, storage and dose measurement technique. The antibiotic suspensions reconstitution and storage handout formed in this study can be used to assist the pharmacist for the daily antibiotic suspensions dispensing and counselling.

# CHAPTER 1

## INTRODUCTION

### 1.1 Background of Study

In primary care settings, antibiotics are among the most prescribed drugs, and their prescribing has increased over the years, especially among young children (Shamsudin *et al.*, 2016). The high frequency of antibiotic use has account for the big expenditure of up to 10.1% of the total drug expenditure (Shamsudin *et al.*, 2016). The prescribing rate of antibiotics was also shown to be higher than the standard of the antibiotic prescribing based on the Malaysian National Medical Care Survey (NMCS) (Tay *et al.*, 2019). Antimicrobial stewardship programs were launched to monitor the appropriate use of antibiotics among government healthcare settings in Malaysia, due to the high usage of antibiotics (Ministry of Health Malaysia, 2019).

A previous study in Malaysia showed that the five most commonly used antibiotics were as follows: amoxicillin being at the top of prescribing list, followed by cloxacillin, erythromycin, bacampicillin and cephalexin (Shamsudin *et al.*, 2016). This usage trend was the same as reported by another study which showed the highest usage of amoxicillin in Malaysian young child (Chan *et al.*, 2006). Amoxicillin is commonly prescribed for upper respiratory tract infections (URTI), including acute pharyngitis and tonsillitis, although the Malaysia National Antibiotic Guideline 2019 suggested that the first line treatment for pharyngitis is phenoxymethylpenicillin and amoxicillin is preferred in the treatment of tonsillitis (Tay *et al.*, 2019). Apart from tonsillitis, amoxicillin is also the first line treatment in infections such as acute bronchitis and pneumonia, acute otitis media and acute rhinosinusitis. Meanwhile,

cloxacillin is commonly prescribed in primary care for the empirical treatment of skin and soft tissue infections, (Ministry of Health Malaysia, 2019).

Antibiotics for paediatric are commonly formulated into dry powders for reconstitution. The lack of antibiotic orodispersible tablets available in the market is one of the reasons. Besides, the formulation of dry powders aim to prevent the hydrolytic degradation of the antibiotic in aqueous vehicle, ease of swallowing for children, and to reduce the cost of transportation (Ali *et al.*, 2019; Mistry *et al.*, 2017; Ola *et al.*, 2018).

The choice of antibiotic formulations in paediatric patients is mainly based on the age-appropriate dosage forms and their acceptability towards that formulation. The age-appropriate formulation is defined as the dosage forms suitable for that age groups. For examples, for children less than 12 years old, minitablets with size of less than 7 mm and solution or suspensions are suitable due to their swallowing ability. The preferable dosage forms for neonates and young child should be suspensions or minitablets with diameter less than 2 mm (Mistry *et al.*, 2017).

On the other hand, the criteria for acceptability of the antibiotic suspensions are the ease of administration and willingness of the patient to take the drug. Normally, dry powder antibiotic suspensions is preferred due to the ease of administration after reconstitution (Ranmal *et al.*, 2018). The willingness of the patients to ingest the antibiotics depends highly on its palatability. The smell, taste and after-taste are important factors that affect the acceptability of the patients. However, the features of smell, taste and after-taste are too subjective and difficult to be assessed. Hence, the

patient's response towards the suspensions that is better than neutral is considered acceptable (Mistry *et al.*, 2017).

Apart from the appropriate antibiotic prescribing and adherence to the clinical guideline, the appropriate use of antibiotics suspensions involves the correct dispensing and administration indicators. The dispensing indicators includes appropriate choice of dose measuring tool, dose measurement technique, dosing frequency, dosing interval and dosing duration. Meanwhile, the administration indicators are correct dry powder antibiotic suspension reconstitution and storage technique (NadeshKumar *et al.*, 2019). Errors from antibiotic reconstitution arise when the parents do not read or understand the manufacturer's instruction. Failure in shaking the bottle to loosen the powder and wrong volumetric measurement technique are among the common reconstitution errors. Besides, wrong steps for the addition of water and wrong choice of water commonly occurred among parents (Al-Ramahi *et al.*, 2015; Olorukooba *et al.*, 2019). In USA, the American Association of Poison Control Centre has reported that in 2018, incorrect concentration of medication administration occurred in around 50% of the child aged less than 5 years old (American Association of Poison Control Centre, 2018).

There are three main factors contributing to incorrect antibiotic dosing: the use of an inappropriate measuring tool, misinterpretation of the dosing label, and incorrect dose measurement technique (Bailey *et al.*, 2009; Yin *et al.*, 2017; Koyama *et al.*, 2019; Vossen *et al.*, 2019; Rashed *et al.*, 2019). Studies showed that medicinal cup and low dose tip syringe with engraved dosing line are two common dose measurement tools for antibiotic suspensions (Al-Ramahi *et al.*, 2015; Olorukooba *et al.*, 2019).

However, dosing variation occurred between these two measuring tools which leads to either overdose or underdose. A previous study demonstrated that around 20% of the medicinal cup measurement exceeded 40% of the actual dose while approximately 40% were underdose (Ouedraogo *et al.*, 2020). Nevertheless, a study showed that the dosing variations were not significant between different types of syringes. (O'Mara *et al.*, 2019). Therefore, syringe is a more suitable measuring tool particularly for small volume antibiotic dosing for paediatrics (O'Mara *et al.*, 2019).

Strict adherence to dosing frequency, interval and duration is essential to ensure the optimal antibiotic therapy. A study from Nigeria reported that around 50% of the parents were unsure about the administration time of the antibiotic although they were told on the frequency of dosing upon dispensing (Olorukooba *et al.*, 2019). Another study from Palestine showed that around 75% of the parents are unsure about the dosing frequency. The dosing of three times daily was misinterpreted as administration of antibiotics following major meals or any three times. Only a quarter of the parents demonstrated the correct knowledge on antibiotic frequency and dosing interval (Al-Ramahi *et al.*, 2015). Besides, some parents misinterpret three times a day dosing as two times a day or every 3 hourly dosing. These wrong dosing intervals may expose the child to risk of toxicity. (Bailey *et al.*, 2009). A study in Malaysia showed that many parents did not adhere to the dosing, duration, and they discontinued the antibiotic administration once their child recover symptomatically (Chan *et al.*, 2006). The wrong duration of administration may affect the treatment efficacy and promote antibiotic resistance. Hence, parents should be advised to complete the whole course of antibiotics. They should be advised on not to keep the remaining antibiotics for the use of other child or for future use (Chan *et al.*, 2006).

The storage of antibiotic suspension after reconstitution is important in preserving the efficacy of antibiotic throughout the treatment period (Ali *et al.*, 2019). The antibiotic dry powders should be stored in an enclosed bottle away from heat, light and humidity. The storage of dry powders at room temperature is deemed suitable as the powders is stable at room temperature (Ola *et al.*, 2018). However, once reconstituted, the suspensions should be stored in the refrigerator to slow down the degradation of the antibiotic. The antibiotic suspension should not be reconstituted all at once but once at a time (Hu *et al.*, 2013). This is due to the chemical and physical instability of antibiotic particles in the aqueous vehicle once reconstituted. For instances, hydrolytic degradations may occur especially for penicillin which has the strain beta-lactam rings (Ali *et al.*, 2019; Ola *et al.*, 2018). In some cases, the lack of refrigerator in the household and the high temperature in tropical country may speed up the degradation of the antibiotic suspensions (Alzomor *et al.*, 2018).

A structured pharmacist-led counselling intervention is among the strategies to address the parents' malpractices of antibiotic reconstitution. A previous study showed that face-to-face counselling between parents and pharmacist with a well-designed photographs-attached education aid was more effective in improving the parents' knowledge of antibiotic suspension (Hu *et al.*, 2013).

## **1.2 Problem Statements**

Currently, only a few international studies have examined common malpractices related to antibiotic use, reconstitution techniques, and storage, with only three key papers identified (Hu *et al.*, 2013; Al-Ramahi *et al.*, 2015, Olorukooba *et al.*, 2019). Moreover, to the best of our knowledge, no study has been conducted on

Malaysian populations investigating this issue. Previous studies showed that there was only a minority of the parents who correctly reconstituted antibiotic suspensions. Majority of the parents wrongly calibrated the volumetric dose of the antibiotic. Previous studies also revealed the poor antibiotic-related knowledge among parents (Al-Ramahi *et al.*, 2015, Olorukooba *et al.*, 2019). It is unsure whether the problems related to antibiotic usage, reconstitution, and storage among parents within rural area in Malaysia is consistent with those from overseas. The lack of knowledge on antibiotic use and technique in antibiotic suspension reconstitution may lead to the inaccurate antibiotic concentrations. This will eventually affect the treatment efficacy, safety and subsequently increase the risk of antibiotic resistance (Olorukooba *et al.*, 2019).

Currently, there are no standardised counselling guide and antibiotic reconstitution handout being developed to aid the counselling of pharmacist particularly to the rural parents. In Malaysia, it was also unknown about the effectiveness of the pharmacist-led counselling towards the parents' practices of antibiotic reconstitution and storage. Furthermore, it was unknown about the acceptance and usability of the counselling guide and handout among the rural parents.

### **1.3 Justification and Significant of The Study**

There is an essential need to develop a structured pharmacist-led counselling guide and parent's education handout on antibiotic reconstitutions. By conducting this study, issues related to antibiotic usage, reconstitution, and storage can be identified and addressed accordingly. Besides, the impact of the pharmacist-led educational intervention was evaluated in this study as well. Upon completion of the study, the

counselling guide and antibiotic reconstitution handout can be disseminated among the government primary health clinics for the standardisation of counselling among pharmacists.

#### **1.4 Research Questions**

- a. What is the impact on the parents' knowledge on antibiotic suspensions reconstitution and storage pre- and post-pharmacist-led educational counselling?
- b. What is the impact on the parent's antibiotic suspensions reconstitution and dose measurement technique pre- and post-pharmacist-led educational counselling?
- c. What is the impact on the parents' knowledge on antibiotic use pre- and post-pharmacist-led educational counselling?
- d. What is the parent's satisfaction towards the pharmacist-led educational interventions on the practices of oral antibiotic suspensions reconstitutions, dosage measurement and storage?

#### **1.5 Conceptual Framework of The Study**

The conceptual framework of this study was developed based on the adaptation of the two models, which are health belief model and trans-theoretical model as shown in figure 1.1. The health belief model is essential in the development of this theoretical framework because this model explains the human health behaviour which includes their belief or perception towards a disease or drugs and their socio-demographic background (Singrist *et al.*, 2013). A previous study showed that parents' belief and access to the dosing tool plays an important role in determining their use of the correct dosing tool for medication dosing in their child. Parents' choice of dosing tool is also associated with limited health literacy and access to pharmacist counselling (Williams *et al.*, 2019). Hence, health belief model can help pharmacist to include parent's belief

and ability in dosing measurement and their needs into account before initiating the counselling session.

The use of trans-theoretical model in this study is also important. This model helps to incorporate, analyse, and explain the health behaviour which assist in the tailoring of counselling and specific interventions to be provided based on parent's perspectives. This model has been used for many years in a wide range of interventions including medication counselling and smoking cessation. This approach has modelled how the pharmacist may interact with the parents in providing the counselling on the correct use of medications (Ficke *et al.*, 2005; Patwardhan *et al.*, 2003).

In this study, this model helps design a counselling session in accordance with the stage of change, which assists pharmacists in addressing the appropriateness of parents' practices regarding antibiotic use. This model also suggests the pharmacists on the specific measures to be taken when interacting with the parents. The incorporation of the concepts in the behaviour of change model and the specific interventions on the parent's practice on antibiotic use can help the pharmacists to utilise this model for the maximum benefits of the patients (Singrist *et al.*, 2013). Hence, the incorporation of these two models is essential as this study involved interventions on parent's malpractice on antibiotic use, antibiotic reconstitution, dose measurement and storage techniques.

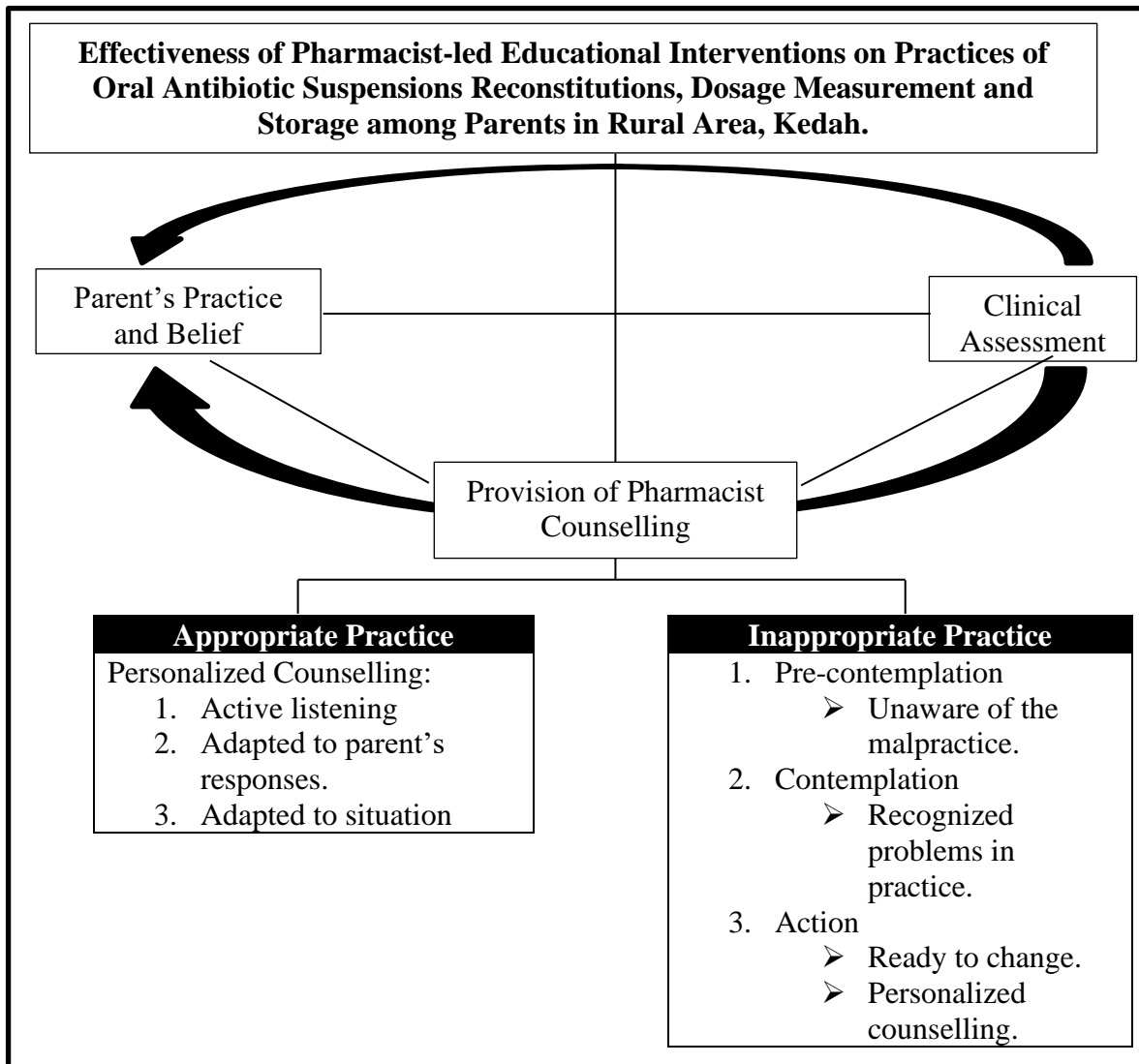


Figure 1.1: Conceptual framework developed and adapted from the health belief model and trans-theoretical with personalised counselling protocol based on parent's practice and belief.

## **1.6 Objectives of the study**

### **1.6.1 General Objective**

This study aimed to evaluate the impact of pharmacist-led educational interventions on practices of oral antibiotic suspensions reconstitutions, dosage measurement and storage among parents in rural area.

### **1.6.2 Specific Objectives**

The specific objectives of this study were as follows:

#### **1.6.2(a) Primary objective**

To assess the improvement in the parent's knowledge of antibiotic suspensions reconstitution and storage pre- and post-pharmacist counselling.

#### **1.6.2(b) Secondary objectives**

- a. To assess the parent's antibiotic suspension reconstitution and dose measurement technique pre- and post-pharmacist counselling.
- b. To evaluate the parent's knowledge of antibiotic use pre- and post-pharmacist counselling.
- c. To determine parent's satisfaction towards the pharmacist's educational intervention.

## CHAPTER 2

### LITERATURE REVIEW

#### 2.1 Introduction

The management of paediatric infectious disease are common among primary care clinicians and are encountered at a daily basis. Most of the infections are viral origin, which does not require specific antimicrobial treatment (Alter *et al.*, 2011). Meanwhile, many infections are bacterial origin and require treatment with antibiotics. Some of the common childhood bacterial infections are acute otitis media, acute otitis externa, streptococcal pharyngitis, acute bacterial sinusitis, and bacterial conjunctivitis, pneumonia, urinary tract infections, acute gastroenteritis, bacterial skin and soft tissue infections (Alter *et al.*, 2011; Gerber *et al.*, 2015).

Extensive clinical history taking, and assessment of the signs and symptoms of the patients are necessary to determine the initiation of an empirical antibiotic therapy (Gerber *et al.*, 2015). Most commonly, the selection of empirical antibiotic therapy is based on the prevalence of commonly caused bacteria for the specific bacterial infection and the local antibiotic susceptibility patterns. The use of empirical antibiotic can also be considered for certain bacterial infections such as sinusitis and otitis media, where the organisms are difficult to be isolated for microbiological culture (Fusco *et al.*, 2019). De-escalation of antibiotic use is necessary if culture and sensitivity results are available later. The streamline of antibiotic prescribing to narrow spectrum antibiotics based on the microbiological culture results may improve the patient's clinical outcome without compromising patient's safety.

The inappropriate use of empirical antibiotics may potentially increase the risk of antibiotic resistance (Alter *et al.*, 2011; Fusco *et al.*, 2019). A previous study showed that the implementation of antimicrobial stewardship program with the development of antibiograms were useful in reducing the cost of therapy and improve clinical outcomes (Al-Sayyed *et al.*, 2017).

## **2.2 Appropriate antibiotic treatment in children**

The choice of antibiotic therapy regimen in children is different than the regimen in adult patients. This is due to the difference in sign and symptoms of the disease, causative organisms involved, choice of antibiotic prescribed, dose, formulations, as well as the monitoring methods (Al-Sayyed *et al.*, 2017; Fusco *et al.*, 2019). There are several considerations and precautions that should be emphasised in the selection of antibiotic regimen such as the physiology of the paediatric patients, antibiotic prescribing and dosing style, choice of formulations, adverse drug reaction profiles and cost (Fusco *et al.*, 2019). The vital signs of neonates, infants and children are very much different from the adult patients. Therefore, clinicians should be more familiarize with the vital signs of paediatric patients across the age continuum to identify the abnormalities in the vital signs (Alter *et al.*, 2011). The poor ability in communication among paediatric patients may also affect the clinician's judgment on their clinical conditions. Hence, the use of non-specific data such as fever, poor oral intake, sleep disturbances, and increased heart rate is essential to detect the abnormalities (Gerber *et al.*, 2015; Fusco *et al.*, 2019).

## **2.3 Appropriate prescribing of antibiotic in children**

Clinicians in the primary care settings play an important role in controlling the antibiotic prescribing among the paediatric patients. The decision for the antibiotic

prescribing should be based on the patient's clinical symptoms, clinician's prior-knowledge of the causative organisms, the local antibiotic resistance patterns, and the culture and sensitivity results if available (Al-Sayyed *et al.*, 2017; Fusco *et al.*, 2019; Rebnord *et al.*, 2017). However, a previous study found that the antibiotic prescribing rate in rural settings was relatively high, reaching up to 23%, with a particular emphasis on the frequent use of broad-spectrum antibiotics (Rebnord *et al.*, 2017).

The overprescribing of antibiotic is common in the primary care setting and is mainly due to several reasons. Many clinicians prescribe antibiotics for fear that they might miss out a serious infection which may need an antibiotic therapy. It has been a challenge for many primary care clinicians to forecast the benefits of antibiotics use. Sometimes, the clinicians might find it difficult to distinguish between an infection that may resolve spontaneously without antibiotic treatment and those that may lead to more severe complications (Rebnord *et al.*, 2017; Hallit *et al.*, 2019). Furthermore, there are pressure from the parents on the clinicians to prescribe antibiotic due to their perceived expectations towards the positive outcome of antibiotic treatment (Hallit *et al.*, 2019). Considering the high patient load and consultation time constraint in the government primary care setting, clinicians may sometimes prescribe antibiotic to save up time for extra explanations to parents on the symptomatic control strategies and the inappropriate use of antibiotics (Hallit *et al.*, 2019). This was also a strategy to avoid lengthy consultation and the need to schedule for further follow-ups (Rebnord *et al.*, 2017). The improper use of antibiotics may increase the potential of antibiotic resistance and bring harmful side effects to the child (Hayhoe *et al.*, 2018). Therefore, interventions should be done to emphasise on the relationship of antibiotic resistance with inappropriate antibiotic use among parents and clinicians (Rebnord *et al.*, 2017).

The variability in prescribing patterns of antibiotics across different primary care settings contributes to the widely use of broad-spectrum antibiotics (Rebnord *et al.*, 2017; Gerber *et al.*, 2015). A previous study found that the prescribing rate of antibiotic in the high-antibiotic-utilization settings were as high as two-fold as compared to low-antibiotic-utilization setting. The patients were four times more likely to receive a broad-spectrum antibiotic therapy (Gerber *et al.*, 2015). This finding reflects that the general prescribing habit is more aggressive towards the use of antibiotics (Gerber *et al.*, 2015). Hence, it is important to have an antimicrobial stewardship program to guide the prescribing of antibiotics among the clinicians (Ministry of Health Malaysia, 2019).

The strict adherence to the antibiotic prescribing guideline and a reduction in the off-guideline prescribing would have an impact of around 10% reduction in the total prescribing of broad-spectrum antibiotics (Gerber *et al.*, 2015). Therefore, the latest Malaysian National Antibiotic Guideline 2019 has included the new chapter on antibiotic prescribing in primary care, which aims to standardize the prescribing of antibiotics among primary care clinicians (Ministry of Health Malaysia, 2019). Education focused on the adherence to antibiotic prescribing guidelines may improve the antibiotic prescribing guideline familiarity among the clinicians and further influence their decisions on antibiotic prescribing (Klein *et al.*, 2017).

#### **2.4 Appropriate dosing of antibiotic in children**

Despite the importance of correct antibiotic prescribing among clinicians, emphasis should also be placed on the appropriate dosage, particularly in paediatric patients. The dosing regimen of antibiotics should be based on patient's age, body

compositions, severity of infections and causative pathogens (Tang *et al.*, 2019; Natale *et al.*, 2017). Paediatric patients are the group of patients aged from birth till 18 years old and the classification of paediatric populations are shown in Table 2.1 (Strickley *et al.*, 2019). The changes of physiology across the age continuum plays an important role in age-related physiological maturation, which has a major impact on the changes of antibiotic pharmacodynamics and pharmacokinetics (Natale *et al.*, 2017). The alterations of antibiotic pharmacokinetics due to physiologic maturation occur mostly in neonates and infants, and the effect continues till childhood. The increase of age may influence the antibiotic dosing in paediatric patients, but the effect decreases later during late childhood and adolescence (Natale *et al.*, 2017). Hence, the classification of paediatric patients based on age is essential prior to the prescribing and dosing guidance of antibiotics (Strickley *et al.*, 2019).

The body compositions of the paediatric patients will also affect the patient's antibiotic dosing. The body compositions are expressed in several measures such as total body weight (TBW), adjusted body weight (ABW), ideal body weight (IBW), body mass index (BMI), and body surface area (BSA) (Natale *et al.*, 2017). Generally, the dosing of antibiotics in paediatric patients are expressed in mg/kg/dose, mg/kg in divided dose, and some may be expressed in terms of BSA (Fusco *et al.*, 2019, Strickley *et al.*, 2019). The maximum paediatrics dose of antibiotic per single dose is normally capped at the single dose of the adult dose. Hence, knowledge on the maximum recommended adult dose is essential to guide the maximum dosing in paediatrics (Fusco *et al.*, 2019). Despite the importance of antibiotics dosing based on body weight in paediatric patients, there were insufficient studies comparing the impact of different weight measuring methods towards the antibiotic treatment outcome. Pharmacokinetic

studies conducted between 1966 and 2015 were compiled and reviewed, revealing that total body weight (TBW) was used for loading dose calculations, while either TBW or adjusted body weight (ABW) was used for maintenance dose calculations for overweight or obese paediatric patients (Natale *et al.*, 2017).

Currently, there are no specific guidelines on the dosing of any specific drugs in either overweight or obese patients (Natale *et al.*, 2017). Commonly, the dosing of antibiotics is based on TBW and BSA in normal-sized paediatric patients (Fusco *et al.*, 2019). However, for overweight and obese patients, the TBW and BSA based dosing is inappropriate as the additional weight, and it does not proportionally equal to the amount of body fat mass and lean body mass. Consequently, the formula for dose calculation based on normal-sized children cannot be extrapolated to these obese paediatric patients (Natale *et al.*, 2017). The use of BMI and IBW in antibiotic dosing may sometimes do not overcome the problems of the variability in weight. Both two measures have taken height differences into account when calculating for patient's weight (Natale *et al.*, 2017; Fusco *et al.*, 2019). A taller child may be mistakenly treated as obese due to the nature of the IBW calculation formula which is much affected by the patient's height (Natale *et al.*, 2017). Besides, IBW is not applicable to child with the height of less than five feet. Therefore, it is not applicable to the dose calculation for obese paediatric patients with the height of less than five feet (Natale *et al.*, 2017; Fusco *et al.*, 2019).

The choice of measures for body size should be individualised based on the patient's condition and the pharmacokinetics profile of the antibiotic (Natale *et al.*, 2017). For example, the use of TBW in the calculation of gentamicin dose causes a

higher dose at around 60% more as compared to the dosing of gentamicin using ABW (Gade *et al.*, 2018). Hence, in the cases of aminoglycosides with narrow therapeutic range, it is suggested that adjusted body weight (ADW) should be used for the calculation of the total daily dose per kilogram bodyweight (Gade *et al.*, 2018; Natale *et al.*, 2017). Conversely, the dosing in penicillin is different from those in aminoglycosides. The pharmacodynamics of penicillin can be improved by increasing the dose or frequency. The pharmacodynamics of penicillin is highly affected by the time when the concentration of the penicillin is above the minimum inhibitory concentration (Gade *et al.*, 2018; Fusco *et al.*, 2019). Therefore, the dosing of penicillin should be based on TBW owing to the wide therapeutic index (Gade *et al.*, 2018).

## **2.5 Choice of formulations for antibiotic use in children**

### **2.5.1 Factors affecting the choice of antibiotics formulation in children.**

Acceptability of the antibiotic formulations among children is important to ensure the antibiotic regimen adherence and targeted therapeutic effects. The definition of acceptability varies across many studies, which includes “ease of administration”, “easy of swallowing”, “patient’s preference”, and “caregiver’s preference” (Ranmal *et al.*, 2018; Strickley *et al.*, 2019). A systematic review involved defined paediatric patients’ acceptability as “the ability and willingness of the patients to take their medicine as intended”. The term “preference” is excluded as part of the definition because the “preference” of one drug over another only shows a relative comparison but do not demonstrate the actual acceptability of the medicine (Ranmal *et al.*, 2018).

The design and choice of formulations for paediatric patients should be adjusted based on their age and the recommendations was summarised in Table 2.1 (Strickley *et*

*al.*, 2019). Liquid oral dosage form is the most used formulations in the market among paediatric patients (Trofimiuk *et al.*, 2019). The preference for the choice of liquid formulation is mainly due to the ease of swallowing. Besides, the safety aspects are also a consideration for drug administration among paediatric patients, which includes the avoidance of choking during drug administration, the convenience of volumetrically measurement of a dose and increase in the chances of the paediatric patients to take the full dose of the drug, especially antibiotics (Strickley *et al.*, 2019; Trofimiuk *et al.*, 2019).

A previous study has shown that the acceptability of liquid oral suspensions was better among paediatric patients. The taste-masking ability of liquid formulations has resulted in the high percentage of acceptability among the paediatric patients (Mistry *et al.*, 2017). Tablet or capsule forms are not suitable for child younger than six years old due to the size of the dosage form and the difficulty to swallow (Trofimiuk *et al.*, 2019). The children ability of swallowing was low particularly among infants (Mistry *et al.*, 2017). A study by Mistry *et al.* found that only half of the infants were able to swallow minitablets up to the dimension of 2 mm while most of the preschool children can swallow minitablets size up to 7 mm in dimensions (Mistry *et al.*, 2017). In order to ease the drug administration in paediatric patient, splitting the capsule or crushing the tablet and mix with food or milk are commonly practise among the parents (Mistry *et al.*, 2017; Trofimiuk *et al.*, 2019). However, the manipulation of the dosage form may cause damage to the drugs, particularly the drugs with modified-release formulations. Therefore, this practice may induce side effects or affect the pharmacological efficacy of the drug (Trofimiuk *et al.*, 2019).

Paediatric oral medication formulations listed in Table 2.1, including orally dispersible tablets, oral powders or granules, mini-tablets, chewable tablets, and oral solutions or suspensions, are all available in Malaysia. However, this study focuses specifically on oral antibiotic suspension formulations.

Table 2.1: Age-appropriate Paediatric Oral Dosage Forms in Primary Care Settings

<b>Age</b>	<b>Classification</b>	<b>Age-appropriate Dosage Forms</b>	<b>Maximum volume of liquid acceptable by patients (mL)</b>
<b>Less than 1 months</b>	Term neonates	Solution or suspensions (ready to use or dry powder or granules for reconstitution)	Up to 0.5
<b>1 month to 1 years</b>	Infants		Up to 2.5
<b>1 – 6 years old</b>	Children (Preschool)	Oral dispersible tablets, oral powder or granules, mini-tablets	2.5 – 5.0
<b>7 – 12 years old</b>	Children (School)	Chewable tablets, oral dispersible tablets	Up to 10.0
<b>13 – 18 years old</b>	Adolescent	Capsules, tablets	-

### 2.5.2 Oral dry powder antibiotic for reconstitution

Liquid oral suspensions can be marketed either in ready-to-use suspensions (such as bromhexine syrup, diphenhydramine syrup and chlorpheniramine syrup) or in dry powder form and to be reconstituted prior to administration (such as antibiotic syrups) (Shamsudin *et al.*, 2016). The antibiotic suspension formulation is a uniform mixture of finely grinded antibiotic in a dry powder form for oral administration (Ali *et al.*, 2019). Table 2.2 summarizes the oral antibiotic suspensions requiring reconstitution prior to administration that are commonly available in the government health clinics in Malaysia (Shamsudin *et al.*, 2016; Pharmaceutical Services Program, 2019).

Table 2.2: The oral antibiotic suspensions that are available in Malaysian government health clinics.

<b>Oral antibiotic suspensions requiring reconstitution prior to administration</b>
Amoxicillin Trihydrate
Phenoxymethylpenicillin Potassium
Erythromycin Ethyl Succinate
Cloxacillin Sodium
Amoxicillin Trihydrate-Potassium Clavulanate
Cephalexin Monohydrate
Ampicillin Trihydrate
Cefaclor Monohydrate

The formulation of antibiotics in dry powder form aims to prevent hydrolysis of the active ingredients (Shamsudin *et al.*, 2016; Ali *et al.*, 2019). The dry powder antibiotic should be reconstituted prior to administration. The dry form protects the antibiotic from hydrolysis, and it maintains the stability of the active antibiotic constituents during the storage period (Shamsudin *et al.*, 2016). Therefore, once the dry powder antibiotic is reconstituted into a suspension, the parents should be reminded regarding the storage conditions of the suspension. Besides, parents should be informed that reconstituted antibiotic suspensions have a shorter shelf life of approximately one to two weeks, compared to non-reconstituted antibiotic powder, which has a longer shelf life of more than two weeks (Ali *et al.*, 2019). The liquid oral suspensions is difficult to be formulated into a controlled release formulation. This might be due to the probability of early release of the active pharmaceutical ingredients (API) of antibiotic in the suspending condition during storage (Shamsudin *et al.*, 2016; Ali *et al.*, 2019). Therefore, the dry powder formulation helps to preserve the chemical and physical stability of the dry powder antibiotic during storage while after reconstitution, the liquid suspension may remain stable along the duration of antibiotic therapy (Ali *et al.*, 2019).

Oral liquid suspension also helps to increase the bioavailability of antibiotic as compared to the traditional tablet and capsule formulations. The antibiotic particles in suspension form will completely be dispersed during the reconstitution state and readily absorbed after administration (Shamsudin *et al.*, 2016; Ali *et al.*, 2019). Besides, the same antibiotic suspension can also be administered to paediatric patients from different age group by adjusting the volume and the dose prescribed (Shamsudin *et al.*, 2016). The dry powder form also provides a lower weight due to the absence of the aqueous vehicle layer. This will ease the transportation process as well as reduces the transportation cost (Ola *et al.*, 2018).

## **2.6 Appropriate antibiotic suspension reconstitution and administration in children**

*Step 1: Shaking the bottle to loosen the powder.*

The first step in the dry powder antibiotic suspensions reconstitution is the shaking of bottle. The shaking of bottle prior to reconstitution is essential to loosen the powder and to prevent sticking or clumping of the powder at the bottom of the bottle (KK Women's and Children's Hospital, 2016). The clumping of the dry powder may be due to the agglomeration properties of the powder. The water facing end of the antibiotic powder will repel the water particles. Consequently, the inner part of the dry powder will neither be easily wetted even with the help of wetting agent in the formulation nor vigorous shaking after reconstitution (Yao *et al.*, 2019, Vega-Zambrano *et al.*, 2019). Therefore, if water is added before loosening of the powder, clumps will form at the bottom of the bottle (Ola *et al.*, 2018).

### *Step 2: Addition of water for reconstitution*

The next step after shaking the antibiotic bottle is the addition of water for reconstitution. Water should be added till halfway of the mark on the antibiotic bottle before shaking for antibiotic suspensions (KK Women's and Children's Hospital, 2016). The parents should be advised on the choice of water and the temperature of water used for reconstitution (Alzomor *et al.*, 2018; Yao *et al.*, 2019; Vega-Zambrano *et al.*, 2019). A previous study done on examining the stability of amoxicillin-potassium clavulanate showed that tap water has some effect on the degradation of antibiotic suspension (Al-Tahami K, 2014). However, the high-performance liquid chromatography (HPLC) assay results showed that the content of amoxicillin and clavulanate is still within the pharmacopeial range which is 90% to 120% (Al-Tahami K, 2014). The degradation of antibiotic in tap water may be due to the high metal content and the acidic pH of the tap water. The presence of high metal content and hydrogen ions in the tap water might promote the hydrolytic degradation of antibiotic suspension (Alzomor *et al.*, 2018; Yao *et al.*, 2019). For example, the antibiotic under the penicillin group contains the strained beta-lactam ring, which is prone to hydrolysis, especially in strong acidic conditions of pH less than 3. The hydrolysis of antibiotic especially the aminopenicillin group such as amoxicillin will produce inactive penicillamic acid and hence affect the efficacy (Al-Tahami K, 2014). However, several studies have shown that the degradation of antibiotic is within acceptable range in different types of water such as treated tap water, distilled water, mineral water, and bottled water (Alzomor *et al.*, 2018; Al-Tahami K, 2014; Vega-Zambrano *et al.*, 2019). Hence, the choice of water may be based on the available source of water (Alzomor *et al.*, 2018; Al-Tahami K, 2014; Yao *et al.*, 2019; Vega-Zambrano *et al.*, 2019). Conversely, the storage condition has more effect on the

degradation on antibiotic suspension after reconstitution regardless of the types of water used (Alzomor *et al.*, 2018; Al-Tahami K, 2014).

The temperature of water used for reconstitution will affect the quality of the final product. The use of boiling water may inactivate the penicillin and hence the use of water at room temperature is suitable for the antibiotic reconstitution (Al-Tahami K, 2014). A previous study showed that at higher temperatures (above 27°C), the antibiotic suspensions changed colour after the addition of boiled water. The change of colour may be because of the suspensions is unstable at high temperature and prone to chemical degradation (Alzomor *et al.*, 2018). In terms of the sedimentation ability of the suspension, the sedimentation rate and volume of the antibiotic suspensions may decrease when the temperature of water used increases (Al-Tahami K, 2014). This is owing to the loss of action of the suspending agent that increase the solubility of the antibiotic suspensions at higher temperature (Alzomor *et al.*, 2018; Al-Tahami K, 2014). Furthermore, microbiology test using agar well diffusion method was used to assess the biopotency of antibiotics suspension reconstituted at different water temperature (Al-Tahami K, 2014). A study by Alforjany *et al.* showed that the antibacterial activity as shown by the zone of inhibition decreases when the temperature of water for antibiotic reconstitution increases (Alforjany *et al.*, 2019). High performance liquid chromatography (HPLC) test was used to investigate the amount of antibiotic loss at 25°C and 80°C (Alforjany *et al.*, 2019). The loss of active ingredient after one hour of reconstitution was 15% higher if reconstitution is using hot water as compared to those with water at 25°C. However, the degradation of antibiotic suspension reconstituted at 80°C slowed down to a further degradation of 1.8% after four days which may be due to the decreased of temperature to room temperature. Therefore, water at room

temperature should be used for the reconstitution of the antibiotic suspensions (Alforjany *et al.*, 2019).

*3. Close the cap tightly and shake the antibiotic suspension to obtain a uniform suspension*

After addition of water, the bottle should be shaken vigorously to disperse the antibiotic particle and to obtain a uniform distribution of the antibiotic particles (KK Women's and Children's Hospital, 2016; Ola *et al.*, 2018). The suspension should be shaken till all the clumps disappear upon visual inspection to ensure the uniformity of the dosage. The packaging of antibiotic dry powder in a bottle with adequate air space above the liquid suspension will provide enough space for mixing of the antibiotic powder with the aqueous vehicle upon shaking the bottle (Ola *et al.*, 2018). The choice of suspending agent is important as it may affect the ease and rate of dispersion of the antibiotic suspension. The suspending agent which requires high temperature or hydration and high shear mixing to obtain uniform mixer is ruled out before manufacturing of the antibiotic dry powders (Ola *et al.*, 2018).

*4. Leave the suspension for 2 to 5 seconds to get rid of the air bubble layer in the bottle.*

The wetting agent such as sodium lauryl sulphate and polysorbate 80 may help to disperse the antibiotic particles optimally at the very low dose. However, the presence of wetting agent will cause the formation of foam or bubbles upon reconstitution and shaking (Ola *et al.*, 2018). Hence, the bottle should be left for 2 to 5 minutes after reconstitution to get rid of the foam or bubble layer before topping up the water to the mark on the bottle (KK Women's and Children's Hospital, 2016; Ola *et al.*, 2018). The addition of water without waiting for the disappearance of the bubble layer may