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## Assessment of microbiological quality of the pediatric oral liquid drugs

**Kaniz Fatema, Sowmitra Ranjan Chakraborty, Tohora Sultana, Md. Mokhlesur Rahman, Niaz Muhammad Kamali, Kamal Kanta Das, Rashed Noor\***

#### ABSTRACT

Present study performed a time course analysis of microbiological contamination level within the pediatric oral liquid drugs commonly available in Dhaka metropolis. Employing cultural and biochemical methods of microbial isolation, the contaminating microorganisms were quantified both from the fresh drugs in sealed bottles and also after 21 days of drug usage. All 20 samples were found to be populated with huge bacteria which were further found to be heightened after 21 days. While fungal presence was nominal during the initial assessment, most of the samples were found to support the fungal growth after 21 days. Staphylococcal growth was observed to be the most predominant after 21 days, followed by the growth of *Klebsiella* spp., *Pseudomonas* spp. and *E. coli*. The study of antibiogram revealed that most of the bacterial isolates were found to be resistant against ampicillin 10 µg, ciprofloxacin 5 µg, amoxicillin 10 µg and piperacillin 10 µg. Other drugs, including ciprofloxacin 5 µg, gentamicin 10 µg, nalidixic acid 30 µg, ceftriazone 30 µg, chloramphenicol 10 µg, erythromycin 15 µg, trimethoprim-sulfamethoxazole 25 µg and erythromycin 15 µg were also found to be ineffective against the bacterial isolates to a moderate extent. Based on the findings of the increase in microorganisms along with the time of usage as well as the proliferation of drug-resistant bacteria with the pediatric drug samples tested, a stringent regulation on the regular microbiological assessment of the drugs is of significance for the sake of consumer safety as well as for the overall public health management.

**Keywords:** Pediatric oral liquid drugs; Microorganisms; Drug-resistance; Consumer safety; Hygiene; Public health.

#### 1. Introduction

Microbial propagation into the pharmaceutical products is not unlikely due to a number of microbial growth influencing parameters including the imperfect good manufacturing practice (GMP) together with the casualty in the total quality management (TQM) especially in the local pharmaceutical industries in the developing countries [1-5]. A huge number of children in the developing countries suffer from the fatality which is unfortunately related to the medical complications, mostly due to lack of unhygienic handling of drugs in oral dosage forms and due to the inappropriate storage condition which in turn accelerates the growth of a range of bacteria and fungi within these non-sterile drugs [1, 3, 6-9]. Oral liquids such as the aqueous solutions, suspensions, emulsions and syrups are used for the pediatric patients [4-5]. Such drugs may provide suitable environment and even may serve as nutrients for the growth and survival of both pathogenic and non-pathogenic microorganisms as they consist of high amount of sugars and moisture [3, 8-10].

In Bangladesh, the quality of drugs in local pharmaceuticals varies significantly and most of them are poorly manufactured [1, 11-13]. Contaminated raw materials and manufacturing water consisting of microbial bio-burden or pyrogens could be a virtuous source of bacterial and fungal contaminations in the pharmaceutical products [1, 3, 4, 5, 14, 15]. Besides, due to the Governmental legislative regulations, especially in the developing countries, a large number of unlicensed and illegal drug stores are selling poorly manufactured pharmaceutical products [1, 3, 16]. For the consumer safety issues, regular examination of the microbiological quality of the products purchased from such stores is of essence.

Oral liquids are usually non-sterile and therefore are likely to harbor different microorganisms, including the harmful ones [3, 4, 12, 17-21]. In this context, children who are comparatively of weak immune system may be further affected upon consumption of such drugs, especially due to the existence of drug-resistant bacteria in the consumed drugs [22].

Another vital issue of the propagation of drug contaminating bacteria lies on the hygienic usage of drugs. Along these lines, present study attempted (1) to determine the initial microbiological contamination level in the fresh pediatric drugs commonly used, (2) to demonstrate the extent of contamination during usage up to 21 days in order to project on the hygienic handling of the drugs, and finally (3) to detect the existence of drug-resistant bacteria in the samples.

## 2. Materials and Methods

### 2.1. Study area, sampling and sample processing

Twenty (20) types of oral liquid drugs with appropriate dates of manufacturing and expiry were collected from different retailer drug stores in Dhaka city, and were transported to the Microbiology Laboratory to assess their microbiological quality. In this context, serial dilution were prepared up to  $10^{-3}$  following the standard methods as described earlier [1, 3, 23]. Spread plate techniques were used for the estimation of total bacterial and fungal load and also to detect the presence of pathogenic microorganisms [1-3, 23].

### 2.2. Enumeration of total viable bacteria and fungi

An aliquot of 0.1 ml of each sample from the dilution  $10^{-3}$  was spread onto the nutrient agar (NA) plates for enumerating total viable bacteria count (TVB) and on Sabourad's dextrose agar (SDA) plates for the estimation of fungal load [1-3, 23]. Plates were incubated at 37 °C for 18 to 24 hours and at 25 °C for 48 to 72 hours, respectively.

### 2.3. Enumeration of specific bacterial pathogens

From the dilution of  $10^{-3}$  of each sample, 0.1 ml of suspension was spread onto the membrane fecal coliform (MFC) agar, MacConkey agar, mannitol salt agar (MSA), and cetrimide agar for the isolation and quantification of total fecal coliform, *Escherichia coli*, *Klebsiella* spp., *Staphylococcus* spp., and *Pseudomonas* spp., consecutively [1-3, 23-25]. MFC agar plates were incubated at 44.5 °C for 18-24 hours, while the other plates were incubated at 37 °C for 24 hours. Presence of *E. coli* was further detected on the eosine-methylene blue (EMB) agar as described previously [2, 23].

#### 2.3.1. Enrichment for *Salmonella* spp. and *Shigella* spp.

Since the cells of *Salmonella* spp. and *Shigella* spp. could be in stressed condition or in viable but non-culturable condition probably due to some endogenous and exogenous factors, enrichment was performed for *Salmonella* spp. and *Shigella* spp. in the selenite cystine broth (SCB) [1, 11, 26-28]. After enrichment, samples were serially diluted up to  $10^{-3}$  from each of the enriched broth (4-6 hour old, 37 °C), and 0.1 ml of suspension were spread from the dilution of  $10^{-3}$  onto *Salmonella-Shigella* (SS) agar, for the isolation of *Salmonella* spp. and *Shigella* spp., and incubated at 37 °C for 24 hours.

### 2.4. Study of antibiogram

To demonstrate the susceptibility pattern of the bacterial isolates to the common antibiotics, the study of antibiogram was performed using on Mueller-Hinton (MH) agar (Difco, Detroit, MI) against ampicillin (10 µg), amoxicillin (30 µg), ciprofloxacin (5 µg), ceftriazone (30 µg), nalidixic acid (30 µg), imipenem (30 µg), erythromycin (15 µg), chloramphenicol (30 µg), trimethoprim/sulfamethoxazole (25 µg), gentamicin (10 µg), and piperacilin (10 µg) by modified Kirby-Bauer method [29, 30]. Cell suspensions of the bacterial

isolates were prepared using MH broth, and after a brief incubation for 4 hours (with the appearance of the turbidity equivalent to the 0.5 McFarland standard), bacterial lawns were prepared over the MH agar, and the antibiotic discs were placed aseptically over the surface. After 12-18 hours of incubation, plates were examined and the diameters of the zones of inhibition were measured (in mm) as described by Ferraro *et al.*, 2001 [31].

## 3. Results and Discussion

Diseased infants and children are often immune-compromised and can be easily affected by the spoilage microorganisms prevailing in the oral liquid drugs used for their medication purposes. The immune-compromised children consuming the microbiologically contaminated drugs might be subject to potential life risk as well as to the heightening of the chance of opportunistic infections. Current investigation thus assessed the growth and proliferation of microorganisms in oral liquid drugs commonly used by the children, and also emphasized upon the extent of microbial contamination upon usage of the drugs in a time course manner.

### 3.1. Prevalence of microorganisms in the pediatric oral drugs tested

Initially all the samples were populated with the total bacterial load of  $10^3$ - $10^4$  cfu/ml while after 21 days, the bacterial prevalence was noticed to be increased up to  $10^6$ - $10^7$  cfu/ml revealing an increase by approximately 3-log in average (Tables 1 and 2). Fungal presence at the initial stage of microbiological assessment was noticed only in one sample, while after 21 days, 16 samples got contaminated with fungi with a bio-burden of  $10^2$ - $10^3$  cfu/ml.

Among the pathogenic bacteria, staphylococcal growth was the most predominant (Tables 1-3). While the initial staphylococcal load was observed in 11 samples ( $10^2$ - $10^3$  cfu/ml), after 21 days, except one sample, all were found to be populated with *Staphylococcus* spp. within a range  $10^2$ - $10^5$  cfu/ml (Tables 1-3). The contamination observed by *Staphylococcus* spp. might occur due to the lack of aseptic handling of the products as well as due to the personnel hygiene; however, their presence is indeed not always regarded as harmful [32-37]. Nevertheless, the staphylococcal presence could be regarded a very sufficient indication of unhygienic handling of products which in turn may trigger the propagation of other bacteria into the oral drugs.

In case of *Klebsiella* spp., initially the prevalence was observed in 6 samples while the prevalence of this bacterium was found to be extended in 10 samples after 21 days ( $10^2$  cfu/ml in 7 samples and  $10^3$  cfu/ml in 3 samples). *Pseudomonas* spp. was found to be present in 4 samples during the initial assessment ( $10^2$  cfu/ml); however, after 21 days, 10 samples were found to harbor this pathogenic bacterium with a load of  $10^3$ - $10^4$  cfu/ml. The initial load of *E. coli* was observed only in one sample while the frequency widened in 9 samples after 21 days with a bio-bio-burden of  $10^2$  cfu/ml in 8 samples and  $10^3$  cfu/ml in one sample. *Klebsiella* spp. is capable of producing pneumonia and gastroenteritis disease like diarrhea, and hence a careful handling of products during consumption is needed. The possible sources of *Klebsiella* spp. might be due to the untreated raw materials and the unhygienic storage facilities [5].

As found in our study, the presence of *E. coli* and *Pseudomonas* spp. in the samples tested could be a major health risk concern [32, 35, 37-39]. Being an enteric microorganism, *E. coli* may be responsible for the gastroenteritis like bloody and watery diarrhea, followed by the onset of post-diarrheal hemolytic uremic syndrome (HUS), a type of kidney failure especially in children under 5 years old. *Pseudomonas* spp. is an

opportunistic human pathogen, most commonly affecting immune-compromised patients, such as those with cystic fibrosis or AIDS [33, 34, 36]. The source of these two bacteria might be the contaminated raw ingredients, manufacturing water, lack of hygienic manufacturing environment, and finally due to the propagation during drug usage as has been observed through our time course study of microbial increase (Tables 1 and 2).

**Table 1:** Initial microbiological load of the oral pediatric drugs.

Samples	TVB (cfu/ml)	Total fungal count	<i>Escherichia coli</i> (cfu/ml)	<i>Klebsiella</i> spp. (cfu/ml)	<i>Staphylococcus</i> spp. (cfu/ml)	<i>Pseudomonas</i> spp. (cfu/ml)
Sample 1	2.3×10 <sup>3</sup>	0	0	0	0	0
Sample 2	5.3×10 <sup>3</sup>	0	0	0	0	0
Sample 3	1.1×10 <sup>3</sup>	0	0	0	0	0
Sample 4	1.5×10 <sup>4</sup>	0	0	0	5.0×10 <sup>3</sup>	0
Sample 5	2.1×10 <sup>4</sup>	0	0	8.0×10 <sup>2</sup>	1.7×10 <sup>2</sup>	1.2×10 <sup>2</sup>
Sample 6	1.0×10 <sup>4</sup>	0	0	1.0×10 <sup>2</sup>	5.0×10 <sup>2</sup>	0
Sample 7	17×10 <sup>4</sup>	0	0	1.1×10 <sup>2</sup>	3.0×10 <sup>2</sup>	0
Sample 8	11×10 <sup>4</sup>	0	0	1.1×10 <sup>2</sup>	1.1×10 <sup>3</sup>	0
Sample 9	9.2×10 <sup>3</sup>	0	0	6.0×10 <sup>2</sup>	2.0×10 <sup>2</sup>	0
Sample 10	1.9×10 <sup>4</sup>	0	0	2.7×10 <sup>2</sup>	0	0
Sample 11	7.5×10 <sup>4</sup>	0	4.0×10 <sup>2</sup>	0	2.0×10 <sup>2</sup>	0
Sample 12	9.9×10 <sup>4</sup>	0	0	0	0	0
Sample 13	9.2×10 <sup>4</sup>	0	0	0	0	0
Sample 14	1.2×10 <sup>5</sup>	0	0	0	1.0×10 <sup>2</sup>	2.3×10 <sup>2</sup>
Sample 15	2.2×10 <sup>4</sup>	0	0	0	1.0×10 <sup>2</sup>	0
Sample 16	2.6×10 <sup>4</sup>	1.2×10 <sup>1</sup>	0	0	2.2×10 <sup>2</sup>	7.0×10 <sup>2</sup>
Sample 17	7.2×10 <sup>3</sup>	0	0	0	0	0
Sample 18	3.6×10 <sup>3</sup>	0	0	0	0	0
Sample 19	4.6×10 <sup>4</sup>	0	0	0	1.0×10 <sup>2</sup>	1.2×10 <sup>2</sup>
Sample 20	5.6×10 <sup>3</sup>	0	0	0	0	0

The experiment has been done in triplicate and the results were reproducible. One representative data has been shown.

\*TVB = Total viable bacteria

*Salmonella* spp. and *Shigella* spp. were completely absent.

**USP limit:**

TVB <10<sup>2</sup> cfu/ml

Absence of specific bacterial pathogens.

**Table 2:** Microbiological load of the oral pediatric drugs after 21 days.

Samples	TVB (cfu/ml)	Total fungal count	<i>Escherichia coli</i> (cfu/ml)	<i>Klebsiella</i> spp.(cfu/ml)	<i>Staphylococcus</i> spp. (cfu/ml)	<i>Pseudomonas</i> spp. (cfu/ml)
Sample 1	1.2×10 <sup>7</sup>	5.5×10 <sup>3</sup>	0	0	5.0×10 <sup>5</sup>	0
Sample 2	7.5×10 <sup>6</sup>	4.5×10 <sup>3</sup>	0	0	1.1×10 <sup>4</sup>	0
Sample 3	1.0×10 <sup>7</sup>	9.0×10 <sup>3</sup>	0	0	2.2×10 <sup>5</sup>	0
Sample 4	2.0×10 <sup>6</sup>	7.5×10 <sup>2</sup>	0	0	1.9×10 <sup>4</sup>	0
Sample 5	4.0×10 <sup>6</sup>	1.0×10 <sup>2</sup>	0	2.4×10 <sup>2</sup>	1.2×10 <sup>4</sup>	1.4×10 <sup>3</sup>
Sample 6	1.4×10 <sup>6</sup>	4.6×10 <sup>2</sup>	2.0×10 <sup>2</sup>	5.0×10 <sup>2</sup>	2.2×10 <sup>3</sup>	2.7×10 <sup>3</sup>
Sample 7	2.3×10 <sup>6</sup>	7.0×10 <sup>2</sup>	1.3×10 <sup>2</sup>	1.0×10 <sup>2</sup>	4.5×10 <sup>2</sup>	2.2×10 <sup>3</sup>
Sample 8	1.2×10 <sup>6</sup>	0	0	4.5×10 <sup>2</sup>	8.8×10 <sup>4</sup>	0
Sample 9	8.0×10 <sup>7</sup>	3.5×10 <sup>2</sup>	1.0×10 <sup>2</sup>	1.0×10 <sup>2</sup>	6.5×10 <sup>2</sup>	8.0×10 <sup>3</sup>
Sample 10	5.0×10 <sup>7</sup>	1.5×10 <sup>2</sup>	1.2×10 <sup>2</sup>	2.0×10 <sup>3</sup>	3.0×10 <sup>4</sup>	0
Sample 11	1.2×10 <sup>6</sup>	2.0×10 <sup>2</sup>	5.0×10 <sup>2</sup>	7.0×10 <sup>3</sup>	1.4×10 <sup>4</sup>	3.5×10 <sup>3</sup>
Sample 12	6.0×10 <sup>7</sup>	6.5×10 <sup>2</sup>	0	6.0×10 <sup>2</sup>	1.8×10 <sup>2</sup>	2.3×10 <sup>3</sup>
Sample 13	4.0×10 <sup>6</sup>	2.0×10 <sup>3</sup>	0	0	0	7.0×10 <sup>4</sup>
Sample 14	2.7×10 <sup>6</sup>	0	1.0×10 <sup>2</sup>	0	2.9×10 <sup>2</sup>	3.8×10 <sup>3</sup>
Sample 15	1.4×10 <sup>6</sup>	0	0	0	2.8×10 <sup>4</sup>	0
Sample 16	2.0×10 <sup>6</sup>	0	0	0	1.0×10 <sup>3</sup>	2.6×10 <sup>3</sup>
Sample 17	9.0×10 <sup>7</sup>	6.4×10 <sup>2</sup>	1.0×10 <sup>2</sup>	0	2.0×10 <sup>3</sup>	0
Sample 18	1.0×10 <sup>7</sup>	7.0×10 <sup>2</sup>	2.0×10 <sup>3</sup>	1.0×10 <sup>2</sup>	1.0×10 <sup>3</sup>	0
Sample 19	2.0×10 <sup>7</sup>	2.4×10 <sup>2</sup>	4.0×10 <sup>2</sup>	1.0×10 <sup>3</sup>	1.5×10 <sup>3</sup>	1.7×10 <sup>3</sup>
Sample 20	2.0×10 <sup>6</sup>	1.3×10 <sup>2</sup>	0	0	1.0×10 <sup>3</sup>	0

The experiment has been done in triplicate and the results were reproducible. One representative data has been shown. *Salmonella* spp. and *Shigella* spp. were completely absent.

\*TVB = Total viable bacteria

**USP limit:**

TVB <10<sup>2</sup> cfu/ml

Absence of specific bacterial pathogens.

**Table 3:** Confirmative biochemical identification of the isolates.

Assumed microorganisms	TSI			H <sub>2</sub> S creation	Indole test	MR test	VP test	Citrate utilization	Motility	Oxidase test
	Slant	Butt	Gas							
<i>E. coli</i>	Y	Y	+	-	+	+	-	-	+	
<i>Klebsiella</i> spp.	Y	Y	+	-	-	-	+	+	-	
<i>Pseudomonas</i> spp.	R	R	-	-	-	-	-	+	+	+
<i>Staphylococcus</i> spp. ssspp.	Y	R	+	+	-	+	-	+	+	-

Y Yellow (Acid)

R Red (Alkaline)

MR Methyl red

VP Voges-Proskauer

### 3.2. Drug-resistance traits of the pathogenic bacterial isolates

Bacterial resistance against the commonly used antibiotics has recently been reported to raise complications in effective medication [22, 40-42]. Such drug resistance trait of microorganisms is a stern hindrance in treating diseases. Among the pathogenic isolates found in our study, the *Pseudomonas* ones were found to be completely resistant against ampicillin 10 µg, ciprofloxacin 5 µg, amoxicillin 10 µg, and moderately resistant against gentamicin 10 µg (Table 4). Like the *Pseudomonas* isolates, the staphylococcal isolates also exhibited 100% resistance against ampicillin 10 µg and amoxicillin 10 µg; and such a complete resistance was also scored against piperacillin 10 µg. Besides, a moderate drug-

resistance attribute of *Staphylococcus* spp. was noticed against ciprofloxacin 5 µg and gentamicin 10 µg. *Klebsiella* isolates were found to be moderately resistant against nalidixic acid 30 µg, ciprofloxacin 5 µg, ceftriazone 30 µg, chloramphenicol 10 µg and erythromycin 15 µg. *E. coli* isolates were exhibited a moderate degree of drug-resistance against ceftriazone 30 µg, and nalidixic acid 30 µg; while a weak extent of resistance was scored against ciprofloxacin 5 µg, chloramphenicol 10 µg, trimethoprim-sulfamethoxazole 25 µg, gentamicin 10 µg and erythromycin 15 µg (Table 4). Thus an array of common drugs was found to be ineffective against the pathogenic isolates, and in other words, almost all the isolates were multi-drug resistant (MDR) [43].

**Table 4.** Antimicrobial susceptibility pattern of the pathogenic isolates.

Isolates Antibiotics	<i>Escherichia coli</i> (n=9)		<i>Klebsiella</i> spp (n=8)		<i>Staphylococcus</i> spp. (n=16)		<i>Pseudomonas</i> spp. (n=7)	
	R	S	R	S	R	S	R	S
AMP (10 µg)	20%	80%	25%	75%	100%	0%	100%	0%
CIP (5 µg)	35%	65%	50%	50%	50%	50%	100%	0%
PIP (10 µg)	20%	80%	25%	75%	100%	0%	0%	100%
CEF (30 µg)	55%	45%	50%	50%	ND	ND	0%	100%
AMO (10 µg)	20%	80%	25%	75%	100%	1%	100%	0%
IPM (30 µg)	10%	90%	0%	100%	25%	75%	0%	100%
CHL (10 µg)	40%	60%	50%	50%	ND	ND	ND	ND
TMP-SUL (25 µg)	40%	60%	25%	75%	25%	75%	25%	75%
GEN (10 µg)	35%	65%	0%	100%	50%	50%	50%	50%
NALI (30 µg)	55%	45%	75%	25%	ND	ND	0%	ND
ERY (15 µg)	30%	70%	50%	50%	25%	75%	ND	ND

All the experiments have been done three times and the results were reproducible. One representative data have been shown. AMP= Ampicillin, AMO= Amoxicillin, CIP= Ciprofloxacin, CEF= Ceftriazone, NALI= Nalidixic acid, IPM= Imipenem, ERY= Erythromycin, CHL= Chloramphenicol, TMP/SUL= Trimethoprim Trimethoprim- sulfamethoxazole sulfomethoxazole, GEN= Gentamicin, PIP= Piperaciline

ND Not done  
N Number of isolates  
R Resistant  
S Sensitive

Overall, as resulted from our investigation, in order to combat against the microbial contamination in the oral drugs, proper implementation of good manufacturing practice (GMP) together with the total quality management (TQM) during product manufacturing in a microbiologically controlled environment, regular quality assessment during distribution and storage of the finished products, and finally the appropriate aseptic handling of the drugs during consumption would be effectual [4, 5, 8, 19, 20].

### 4. Conclusion

Pediatrics oral liquid drugs are for infants and children and therefore the presence of pathogenic microorganisms is undesirable. The current investigation revealed a huge extent of microbial contamination including the drug-resistant ones within the tested samples especially in course of their exposure

during usage. Such an incidence is very much likely to lead the infants and the children to be easily infected by microorganisms propagated from these drugs during medication. Therefore, stringent regulatory actions on the microbiological quality control together with the personal hygienic improvement would be effective for the better management of the overall public health situation not only in Bangladesh but also in the other developing countries.

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### 6. Conflicts of Interest

Authors have declared no conflict of interest

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