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RESEARCH ARTICLE

# A Review of the Ingredients Contained in Over the Counter (OTC) Cough Syrup Formulations in Kenya. Are They Harmful to Infants?

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**Citation:** Kigen G, Busakhala N, Ogaro F, Chesire E, Saat N, Too R, et al. (2015) A Review of the Ingredients Contained in Over the Counter (OTC) Cough Syrup Formulations in Kenya. Are They Harmful to Infants? PLoS ONE 10(11): e0142092. doi:10.1371/journal.pone.0142092

**Editor:** Imti Choonara, Nottingham University, UNITED KINGDOM

**Received:** June 19, 2015

**Accepted:** October 16, 2015

**Published:** November 5, 2015

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**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** The authors have no support or funding to report.

**Competing Interests:** The authors have declared that no competing interests exist.

**Abbreviations:** OTC, Over the counter; MTRH, Moi Teaching and referral Hospital.

## Abstract

### Background

Cough syrups are widely used in the developing world, but safety of their use in infants and children less than two years has not been well documented. Some syrups contain multiple combinations of such drugs as promethazine, diphenhydramine and ephedrine; which are individually now contraindicated in children less than two years. Despite this, the syrups are available as over the counter drugs and may be dispensed to mothers who are unaware of the potentially hazardous effects to their infants. A descriptive cross-sectional study was used to investigate suitability of cough syrups sold within Eldoret municipality for use in children less than two years of age based on their formulations and available literature.

### Methods

Two semi-structured questionnaires were administered to pharmacy attendants and mothers attending sick child clinic at a referral hospital to establish whether cough syrups containing more than one active ingredient of compounds, now contraindicated in children are administered to infants, and awareness of potential serious adverse effects. Data from labeled contents of cough syrups from retail pharmacies was recorded and corroborated with information from literature to determine those deemed to contain the ingredients. The second questionnaire was administered to mothers with children less than two years to ascertain whether they had used the identified syrups. A total of 260 mothers and 55 pharmacy attendants were interviewed.

## Results

There was widespread use of the syrups in children, including infants, with 192 (74%) of the respondents having used identified syrups and over 90% of these on children less than 2 years including those less than three months. 146 (76%) mothers had administered the syrup at double the recommended dose.

## Conclusion

The regulatory authorities should make concerted efforts to discourage use of cough syrups containing ingredients that pose adverse events to infants, including campaigns to educate pharmacy workers and mothers.

## Introduction

Over the counter (OTC) cough and cold preparations are some of the most widely used medications in Kenya, just like in many other parts of the world. They are used in the treatment of common conditions such as allergies including urticaria, allergic rhinitis and common cold in both children and adults [1,2]. They mainly contain combinations of antihistamines, antitussives, decongestants and expectorants, in various proportions. However the benefits of their use in infants has recently generated debate, especially considering that some of the cough preparations containing antihistamines have been associated with serious adverse effects [3–5]. The current view is that antihistamines should not be used in infants, and some researchers have even suggested that 1<sup>st</sup> generation antihistamines should no longer be dispensed as OTC medicine, owing to their adverse effects [6–8]. In addition, the fact that they are sold as OTC medicine further complicates the issue especially in developing countries whereby regulation of drugs is still of major concern. In fact, the American College of Chest Physicians (ACCP) and US Food and Drug Administration (FDA) have both recommended that OTC cough and cold products should not be used in infants and children under 2 years old [9,10].

There are several generic syrup preparations available in the Kenyan drug shops from various manufacturers which contain more than one active ingredient which are sold as OTC drugs. These include those containing a combination of up to three anti allergic drugs; promethazine, diphenhydramine and ephedrine in various proportions as the main active ingredients. These preparations are quite popular because they are cheap and readily available. However the rationale for the use of a combination of three drugs with similar functions in one product is unclear. In addition, promethazine and ephedrine have serious toxicity profiles. The products do not also contain warning labels barring their use in infants, despite the fact that all the three drugs are contraindicated in children less than two years [11–14]. Some even contain an extra antihistamine, chlorpheniramine to make a total of four antiallergic drugs in one preparation.

Promethazine is a first-generation antihistamine with strong sedative, antiemetic and anticholinergic properties. It is widely used as an antihistamine, a sedative as well as antiemetic [15]. However serious adverse effects including fatal respiratory depression, sleep apnea, oversedation, agitation, seizures, hallucinations, and dystonic reactions have been reported with its use. Other adverse effects include cardiac arrests and neuroleptic malignant syndrome [16]. This led to withdrawal of its use in children less than 2 years in America in 2004, and strengthened warning (boxed warning) in children over 2 years [12,13,17–19]. Promethazine is

therefore not recommended to be used in children less than 2 years, and this warning is contained in the manufacturers manual [20].

Diphenhydramine is a first-generation antihistamine with anticholinergic, antitussive, antiemetic and sedative properties that is mainly used to treat allergies and common cold. It is also used in the management of drug-induced Parkinsonism and other extrapyramidal symptoms. The drug has a strong hypnotic effect and has been approved as a non-prescription sleep aid [21]. The adverse effects associated with diphenhydramine include sedation, motor incoordination, epigastric distress, dizziness and thickening of bronchial secretions. Case report studies conducted in USA regarding diphenhydramine monotoxicity concluded that the most common symptoms for all cases were cardiac dysrhythmias, seizure activity, and/or sympathetic pupil responses. The most common autopsy finding was pulmonary congestion [11,22,23]. This led to its contraindication in neonates, premature infants and breastfeeding mothers [24].

Ephedrine is a sympathomimetic drug used as a decongestant and bronchodilator in treatment of allergic disorders, asthma and hypotension associated with anaesthesia. It is also an appetite suppressant, concentration aid and a stimulant. Ephedrine is found in various plants in the genus *Ephedra* and is structurally similar to epinephrine, phenylpropanolamine and methamphetamine, an illicit drug of abuse. The drug has therefore been clandestinely used as a performance enhancing drug and to manufacture methamphetamine [25–27]. Its adverse effects, especially associated with an overdose include nervousness, insomnia, vertigo, headache, tachycardia, palpitations and convulsions. Serious adverse effects have been observed with its use in children [14]. Orally administered ephedrine is therefore only recommended for use in children less than 12 years under prescription as per the manufacturer's instructions [28–30].

From the existing literature, it is therefore inappropriate that three drugs which are individually not recommended, or recommended to be used with caution in children, can be combined in one formulation and administered freely to children, including infants. The aim of our research was to investigate the chemical formulations of the OTC cough preparations in the Kenyan market and to establish the safety of their use in children, especially infants; based on currently available literature. We also determined the rate and frequency of their use in children less than two years and the factors influencing the choice of these drugs. Additionally, we sought to ascertain whether the attendants working in the retail pharmacies are aware of the fact that cough syrups containing some specific ingredients should not be administered to children less than two years.

## Materials and Methods

Permission to conduct the research was obtained from the Institutional Research and Ethics Committee [31], of Moi Teaching and Referral Hospital (MTRH) and Moi University (*approval ref FAN:IREC 1211*). All efforts were made to protect the privacy and anonymity of the participants throughout the study. The committee allowed the use of verbal consent from the mothers/caretakers of the children as the study was only descriptive with minimal risk to the subjects and did not require disclosure of their identities. Across-sectional descriptive study was adopted, with all the mothers/caretakers attending outpatient paediatric clinic with children less than 2 years of age, and pharmacy outlets within Eldoret municipality included in the study. Mothers attending paediatric clinic with children over 2 years were excluded. Any other drug preparations administered to the children that were not cough syrups such as antibiotics, antipyretics and pain killers were also excluded. Simple random sampling was used to determine the target sample of the pharmacies, while systematic sampling procedure was employed in order to identify the number of mothers required for the study. We obtained information

from the Ministry of Health that the number of registered pharmacies in Eldoret town then was 127. Fisher's formula was used to determine the number of pharmacies to be included in the study, and a sample size of 55 was arrived at. Similarly, the equation was used to calculate the desired sample size of the mothers to be included in the study. From the MTRH records, average the number of mothers attending the pediatric clinic is about 2000 per month, with 800 having children less than 2 years. Using the formula then, the desired sample size was calculated to be 260.

## Data collection

This was done through questionnaires and semi structured interviews which were administered to the participants. In order to establish whether the syrups were used by infants and children less than two years, two sets of questionnaires were used to collect data on cough syrup use from both pharmacies and mothers attending the sick child clinic at MTRH ([S1](#) and [S2](#) Figs). The first questionnaire was administered to attendants working in the pharmacies to ascertain the composition of the cough syrups in their premises, and to select those whose formulation fitted into the category of cough syrups containing more than one active ingredient, or contraindicated in infants. It was also used to establish the rate and frequency of use of these syrups; and to ascertain whether the attendants were aware of risks associated with their use in children, especially infants. The composition and strength of the syrups, brand names, cost, batch numbers and country of origin, manufacturer, and labeled contents of all the cough syrups available in the outlets were recorded. The toxicity profiles of the formulations were then corroborated with information available from literature, and each of the syrups identified to fit in the category of cough syrups containing more than one of the now contraindicated active ingredients was then photographed and anonymized.

The second questionnaire was administered to mothers attending the outpatient pediatric clinic at MTRH to ascertain whether they had used any of the identified syrups, or any other cough preparations that were deemed to be contraindicated in infants based on the results from the first questionnaire. The photographs obtained from the first questionnaire, or empty bottles/packets were used assist the mothers in the identification of the syrups. Details of the type of syrup administered, age of child when the syrup was administered, dosage administered and reason for purchase of the syrup were subsequently recorded. The frequency of the syrup use in children less than two years of age was also recorded.

## Statistical analysis

Cough syrups were grouped according to their ingredients. The ingredients and quantities were determined and compared to the recommended levels in order to ascertain their suitability. For each category of syrups, the frequency of use in children aged less than two years was determined. The extent to which cough syrups containing these ingredients was administered to children less than 2 yrs, and frequency of use of these drugs was then established. The level of awareness of the pharmacy staff about the risk predisposed by use of these drugs on children less than 2 years was also determined. A chi-square test was used to assess the association between caretaker's level of education, type of drug used and dosage levels at 5% level of significance.

## Results

A total of 260 mothers attending the sick child clinic at MTRH, and attendants from 55 pharmacies at Eldoret municipality were interviewed. The compositions, strengths, labeled instructions and costs of the identified syrups are as illustrated in [Table 1](#).

**Table 1. List of the compositions of identified syrups cough syrups containing more than one active ingredient.**

Syrup	Cough syrup				Cost (Ksh)		Instructions on the bottle
	Diphenhydramine HCl	Promethazine HCl	Ephedrine HCl	Chlorpheniramine	60 ml	100 ml	
<b>A</b>	5mg	2.5mg	7.5mg		45	60	- Children under 3yrs-2.5ml 2 to 3 times daily- Children 3–12 yrs - 5ml 3times daily
<b>B</b>	5mg	2.5mg	7.5mg		60	90	- Children below 2 yrs - Not recommended - Children 2–6 yrs - as prescribed by physician
<b>C</b>	5mg	2.5mg	7.5mg		50	90	- Children 1-6yrs - 2.5ml 3–4 times a day- Children 7-12yrs - 5ml 3–4 times a day
<b>D</b>	5mg	2.5mg	5mg	2.5mg	60	90	- Children 2-5yrs-2.5ml every 6 to 8 hours - Children 6–12 yrs - 2.5ml every 4 to 6 hours
<b>E</b>	5mg	2.5mg	7.5mg		60	90	- Children 2-5yrs - 2.5mls 3–4 times a day or as directed by physician- Children 6–12yrs - one 5mls 3 to 4 times a day
<b>F</b>	5mg	2.5mg	7.5mg		50	80	- Children 2-6yrs - 2.5ml every 3–4 hours or as directed by physician- Children 6-12yrs - 5ml 3–4 hours
<b>G</b>	5mg			2mg	60	80	- Children - 2.5ml to 5ml every six hours or as recommended by the doctor
<b>H</b>			7.5mg	2mg	60	90	- Children under 2yrs -Not recommended - Children 2–6 yrs - As prescribed by the physician
<b>I</b>	10mg	5mg			50	70	- Children 2–6 yrs - As directed by the physician- Children 6 to 12 yrs - 5ml 3–4 times a day

doi:10.1371/journal.pone.0142092.t001

The syrups were identified by alphabetical letters (A-G). A total of nine syrups were identified to contain a combination of promethazine, diphenhydramine and chlorpheniramine in various proportions. Out of these, five (A, B, C, E & F) contained 2.5 mg of promethazine, 5 mg of diphenhydramine and 7.5mg of ephedrine per 5mls. Syrup D had a lower amount of ephedrine (5mg) but had in addition 2.5mg of chlorpheniramine to make a total of four active ingredients in one preparation. Syrups G, H & I had two ingredients each; diphenhydramine and chlorpheniramine in G, ephedrine and chlorpheniramine in H and diphenhydramine and promethazine in I. Syrup C had instructions allowing for use in children under two years (2.5ml three to four times daily), syrup A in those under 3 years (2.5ml two to three times daily), whereas all the others had instructions for use in children aged two years and above. The average cost the syrups was about one US dollar (90 Kenya Shillings) per100ml (Table 1). All the identified syrups were manufactured in Kenya, but we also got to learn that most of the ingredients were imported, mainly from India.

192(74%) of the respondents had administered at least one of the identified syrups to their babies, with the most popular being syrup A with 91(36%) having administered (Table 2).

The syrups were mainly administered to infants belonging to the age bracket of 6–12 months (96, 50%), but notably (82, 43%) were administered to those aged 3–5 months, including infants as young as 2 months (5, 2%). Nine (5%) of the children who used the identified syrups were in the age bracket of between one and two years. The most popular dosage was one teaspoonful three times a day, with 146(76%) of the respondents having administered, which is double the recommended dose of 2.5ml three to four times daily.

There was no significant association between the dosage use and level of education of mother/care giver ( $\chi^2 = 7.105$ ,  $df = 4$ ,  $p = 0.131$ ). 92% of the mother's with primary level of education administered a dose of one teaspoonful three times a day whereas 80% of those with secondary education and 50% of those with tertiary education used the same dose. Advice from

**Table 2. Details on the sex of the children, highest level of their mother’s education and proportions of those who have used any of the identified syrups, as well as the type of syrup.**

Question		Number	%
Sex of the baby	M	141	54
	F	119	46
Mother’s highest level of education	1°	59	23
	2°	128	49
	3°	73	28
Ever administered any of the identified syrups to baby?	Yes	192	74
	No	68	26
Listed Syrup	A	91	36
	B	36	15
	C	27	11
	D	23	9
	E	14	5
	F	9	4
	G	9	4
	H	5	2
	I	5	2
	A&D	18	7
A&B	14	5	

1° - Primary school level of education

2° - Secondary school level

3° - Tertiary level (university, technical colleges etc).

doi:10.1371/journal.pone.0142092.t002

the pharmacy attendants was identified as the leading factor which influenced the choice of syrup ([Table 3](#)).

## Discussion

Cough and cold products have been used in paediatric patients for many years to provide relief for the uncomfortable symptoms. However, several reports from trials conducted in children have concluded that there are no significant benefits of using the syrups over placebo. On the contrary, this may predispose the children to serious adverse effects, especially those less than two years of age [32–36]. To this extent, the regulatory authority in America in January 2008 withdrew some of the OTC cough products, or restricted their use in children, especially those

**Table 3. Factors that influenced choice of the syrup.**

	Reason for purchase	Number	%
A	Advice from the pharmacy attendant	155	43
B	Cost	68	19
C	Efficacy, based on past use	32	9
D	Other reasons (e.g. friend told her)	9	3
A&B		55	15
A&C		18	5
B&C		14	4
A,B&C		14	4

doi:10.1371/journal.pone.0142092.t003

under the age of 2 years due to serious and life threatening adverse effects [9,35]. The position of the American Academy of Pediatrics has since then been that the syrups do not work in children less than 6 years, and that their misuse could cause serious adverse effects. It has also recommended further research on the efficacy of all cough and cold medications used in children. The Canadian Paediatric Society also holds the same views, according to a report released in November 2011, and both have provided other options for parents and caregivers for the management of cold symptoms including use of saline water, fluid intake, humidified air (vaporizer), honey and acetaminophen if accompanied by fever [37,38].

The current view based on recently conducted studies in several other centres is that the use of cough syrups should be restricted in children owing to concerns on both efficacy and safety, and that other safer remedies such as honey should instead be used [32,39–43]. Authors from a study conducted recently in Kenya arrived at the same conclusions [43,44]. However, despite international warnings, cough and cold medications including those with potentially harmful ingredients are still used in children, including those aged below 2 years in many parts of the world [45,46].

Our findings indicate that OTC cough syrups containing more than one of these ingredients, especially antihistamines are still widely used in Kenya. It is also worth noting that the regulatory body in Kenya, the Pharmacy and Poisons Board (PPB) in its website maintains that OTC cough and cold medicines are not recommended in children less than two years unless with specific prescription from a doctor [47]. The OTC syrups listed as not recommended for children less than six years of age include antitussives (dextromethorphan and pholcodine), expectorants (guaifenesin and ipecacuanha), nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline), and antihistamines [brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, promethazine and tripolidine] [47]. Despite this, our findings indicate that they are not only still in use in children under six years, but also in multiple combinations. Of major concern is the dosage whereby 76% of our respondents had administered the syrups at a dose of 5mls three times a day, which is a high dose even if the syrup was suitable for the infants. Parental misunderstanding including poor numeracy skills has been described as one of the components leading to overdosage and toxicity of OTC cough syrups [48].

Most of the pharmacy attendants whom we interviewed were not comfortable when we inquired about their level of education. This could be attributed to the fact that there was an ongoing crackdown on unlicensed pharmacies at the time by the regulatory authorities. Many (60%) were however not aware that the ingredients we sought were harmful to children, especially when administered in combinations. According to them, the most important factors which influenced the sale of a specific syrup was cost (40%), duration in the market (30%) and the aggressiveness in marketing by the manufacturer (25%). We were informed that some manufacturers provided incentives such as discounts and credit facilities to the outlets. Advertisements of drugs, easy access by patients to community pharmacies and consumer freedom have also been reported as some of the factors contributing to abuse of OTC drugs [49,50].

## Conclusion

The regulatory bodies in Kenya need to revise their list in line with international recommendations and enforce this policy. Production of syrups with multiple antihistamine preparations or other ingredients now contraindicated in infants should also be discouraged. Concerted education or awareness public campaigns on the effects of these syrups should also be undertaken particularly to pharmacy attendants and mothers.



## Supporting Information

**S1 Fig. Questionnaire 1 (administered to the staff dispensing the drugs at the drug shops).**  
(TIF)

**S2 Fig. Questionnaire 2 (administered to mothers/caretakers attending MTRH paediatric clinic).**  
(TIF)

## Author Contributions

Conceived and designed the experiments: GK. Performed the experiments: GK EC NS. Analyzed the data: GK NB FO RT WN. Contributed reagents/materials/analysis tools: GK NB FO EC NS RT WN. Wrote the paper: GK RT WN.

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