Pharm Res (2011) 28:484–489
DOI 10.1007/s11095-010-0289-1

COMMENTARY

Counterfeit Medicines in Cambodia—Possible Causes

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Received: 13 July 2010 / Accepted: 17 September 2010 / Published online: 1 October 2010

KEY WORDS Cambodia · counterfeit medicine · developing country · factors · quality

INTRODUCTION

The use of counterfeit medicines present a world-wide public health crisis (1). Although few reports are available on the global consequences of counterfeit medicines, the consequences of the issue are enormous, and people could be at considerable risk if they use counterfeit medicines (2,3).

The epidemiology data is often limited. Data compilation and comparison is difficult due to the fact that different methods are used to produce the estimates. In developed countries, less than 1% of medicines are estimated to be counterfeits; however, the evidence suggests that the percentage is much higher in developing countries, where regulatory systems and their enforcements are weakest (4).

The prevalence of counterfeit and substandard medicines reported in Cambodia ranges from 4% to as high as 90% from 2001 to the present (5–8). To tackle the situation, the Ministry of Health of Cambodia initiated a collaborative project with Kanazawa University and Japan Pharmaceutical Manufacturers Association (JPMA), Japan in 2006 to assess the prevalence of counterfeit pharmaceutical products and to investigate factors that influence counterfeiting.

METHODS

In 2006, amoxicillin, ampicillin, cephalexin, paracetamol, artesunate and chloroquine were sampled. In 2007, similar samples of 2006, except artesunate and chloroquine, were collected, and in 2008, anti-helminthics albendazole, mebendazole and metronidazole were collected. In Cambodia, licensed drug outlets are categorized into Pharmacy, Depot-A and Depot-B. A Pharmacy outlet is run by a registered pharmacist, a Depot-A outlet by an assistant pharmacist (who received 3 years pharmacy training), and a Depot-B outlet by a doctor or retired nurse (9). Approxi-

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mately equal numbers of medicines were collected in each year from 2006 to 2008 from urban and rural private drug outlets (i.e.: Pharmacy, Depot-A, Depot-B, and non-licensed outlets) through a stratified random sampling scheme. Samples of the urban areas were collected from the seven districts of the capital, Phnom Penh, whereas the rural samples were collected from three provinces: Kandal, Takeo and Kampong Spue. These locations were selected taking into account of the density of population, concentration of drug outlets, and budgetary limitations and in consultation with the Department of Drugs and Food (DDF) and the National Health Product Quality Control Center (NHQC). The first drug outlets in each location were selected based on their proximity to national roads, and subsequent outlets further away were visited until the end of the sampling hours.

Two sampling teams deployed for the sampling activities were comprised of a research investigator, a locally recruited sampling officer, and a sampling assistant. The locally recruited members were provided with training before sampling and instructed to purchase medicines as average customers. After payment of the purchased medicines in an outlet, the sampling officer filled in a sampling form for each of the samples. Samples were transported taking temperature controlled measures and preserved at 20–25°C until analyzed.

The methodology of the authenticity investigation and the registration verification was adopted from the World Health Organization (WHO) (8). The pharmaceutical quality of the samples was assessed by High Performance Liquid Chromatography (HPLC) and dissolution test at the NHQC in Cambodia and in Kanazawa University, Japan according to a standard monogram. HPLCs were conducted by HITACHI and Agilent HPLC series 1100, and as such, the United States Pharmacopeia (USP) 28 was followed for amoxicillin, paracetamol, chloroquine, albendazole, mebendazole and metronidazole; Japanese pharmacopoeia was followed for ampicillin; the International Pharmacopoeia was followed for artesunate; and British Pharmacopoeia was followed for cephalexin. Dissolution tests were conducted by NTR-VS6P dissolution tester of Toyama Sangyo Co. Ltd., and as such, USP 27 was followed for amoxicillin, and USP 30 was followed for ampicillin, cephalexin and paracetamol.

Data analysis was performed using SPSS release 17.0.0 (Chicago: SPSS Inc.). When appropriate, Fisher's exact test was used to test the significance of categorical variables, and logistic regression analysis was conducted to identify significant factor responsible for the dependent variable. Statistical significance was evaluated at the 5% level.

RESULTS

At the end of this 3-year study, a total of 710 samples (2006: 253; 2007: 254; 2008: 203) were collected. Of the 710 samples, 135 (19.0%) were amoxicillin, 121 (17.0%) were ampicillin, 111 (15.6%) were cephalexin, 136 (19.2%) were paracetamol, 3 (0.4%) were chloroquine, 1 (0.1%) were artesunate, 68 (9.6%) were albendazole, 56 (7.9%) were mebendazole and 79 (11.1%) were metronidazole (Table 1). Around half of the samples (50.3%, 357) were collected from Phnom Penh, while the rest were from provinces. A majority (64.1%, 455) of the samples originated from outside of the country. The packaging condition of 54.6% of the samples was intact during sampling, whereas the rest were open.

Drug Outlets

Of the total samples, 27.9% (198) were collected from 117 Pharmacy outlets, 17.6% (125) from 62 Depot-A outlets, 28.2% (200) from 119 Depot-B outlets and 26.3% (187) from 107 non-licensed outlets. The proportion of non-licensed outlets was higher in the rural areas compared to urban areas: 43.3% of the rural *vs.* 16.5% of the urban in 2006, 42.6% *vs.* 27.0% in 2007, and 26.9% *vs.* 11.4% in 2008. Significant association was found between the licensing status of the outlets and the area of their distribution (Fisher's exact test: $p<0.001$). Registered pharmacists were present in 24.8% (29/117) of the Pharmacy outlets, and only 1.5% (6/405) of the outlets had air conditioning. Statistically significant association was observed between samples from open containers/packs and Pharmacy outlets without having any registered pharmacist on the duty (Fisher's exact test, $P<0.05$).

Registration

Among all the samples, 69.9% (496/710) were registered by the DDF. Registration increased from 62.5% (158/253) in 2006 to 72.4.1% (173/239) in 2007 and 84.2% (165/196) in 2008. However, 68 (9.6% of the collected samples) of the non-registered samples had registration labels on their outer packages. Registration status could not be verified for 22 samples (3.1%) due to insufficient information. Of the registered samples, the largest proportion, 28.6% (142/496), was collected from Pharmacy outlets, whereas the largest proportion (30.7%, 59/192) of the non-registered samples were collected from Depot-B outlets. Among 191 unregistered samples, 75.4% (144) were foreign origin (Fisher's exact test, $p<0.05$).

Table 1 Characteristics of the Samples by Years

	2006	(%)*	2007	(%)*	2008	(%)*	Total	(%)
Name of the medicines sampled								
Amoxicillin	69	(27.3)	66	(26.0)			135	(19.0)
Ampicillin	61	(24.1)	60	(23.6)			121	(17.0)
Cephalexin	52	(20.6)	59	(23.2)			111	(15.6)
Paracetamol	67	(26.5)	69	(27.2)			136	(19.2)
Chloroquine	3	(1.2)					3	(0.4)
Artisunate	1	(0.4)					1	(0.1)
Albendazole					68	(33.5)	68	(9.6)
Mebendazole					56	(27.6)	56	(7.9)
Metronidazole					79	(38.9)	79	(11.1)
Total sampled	253		254		203		710	
Package condition during sampling								
Sampled from Intact pack/container	253	(100)	78	(30.7)	57	(28.1)	388	(54.6)
Loose medicine/open pack/container	0		176	(69.3)	146	(71.9)	322	(45.4)
Categories of drug outlets								
Pharmacy	66	(26.1)	69	(27.2)	63	(31.0)	198	(27.9)
Depot A	47	(18.6)	35	(13.8)	43	(21.2)	125	(17.6)
Depot B	70	(27.7)	70	(27.6)	60	(29.6)	200	(28.2)
Non-licensed	70	(27.7)	80	(31.5)	37	(18.2)	187	(26.3)
Sampling location								
Urban (Phnom Penh)	131	(51.8)	125	(49.2)	101	(49.8)	357	(50.3)
Rural (Provinces)	122	(48.2)	129	(50.8)	102	(50.2)	353	(49.7)
Registration status		*/**		*/**		*/**		**
Registered	158	(62.5)	173	(72.4)	165	(84.2)	496	(72.1)
Not registered	95	(37.5)	66	(27.6)	31	(15.8)	192	(27.9)
Unknown (inadequate information)	0		15		7		22	
Labeled origin								
Domestic	93	(36.8)	72	(29.8)	73	(36.9)	238	(34.3)
Foreign	160	(63.2)	170	(70.2)	125	(63.1)	455	(65.7)
Unknown (inadequate information)	0		12		5		17	
HPLC result								
Passed	243	(96.4)	232	(91.3)	173	(100)	648	(95.4)
Failed	9	(3.6)	22	(8.7)	0		31	(4.6)
Not-done	1		0		30		31	
Dissolution result								
Passed	222	(89.2)	214	(94.3)			436	(91.6)
Failed	27	(10.8)	13	(5.7)			40	(8.4)
Not-done	4		27		203		234	
Samples failed in both HPLC and Dissolution	4		5				9	
Authenticity result								
Authentic	180	(99.4)	160	(95.8)	158	(95.8)	498	(97.1)
Counterfeit	1	(0.6)	7	(4.2)	7	(4.2)	15	(2.9)
Not available	72		87		38		197	

* % among total in an individual year, ** % among verified samples

Authenticity Investigation

We received responses from 65% (35/54) of the manufacturers for the samples of 2006, 42% (24/57) for 2007, and 70% (28/40) for 2008. Responses from Medicine Regulatory Authorities (MRAs) were received from 55% (6/11) of the countries in 2006, 53% (8/15) in 2007, and 82% (9/11) in 2008. Among received replies regarding 513 samples, 15 (2.9%) were identified as counterfeit. Of the counterfeit samples, one was albendazole, four were amoxicillin, two were ampicillin, six were mebendazole, and two were paracetamol. Most (14) of the counterfeits were collected from open packages or containers and/or originated outside of the country (Fisher's exact test, $p<0.05$). A majority (73.33%, 11/15) of the counterfeits were non-registered. Detailed characteristics of counterfeits are illustrated in Table 2. A logistic model was prepared with 512 samples for analysis of the influencing factors, and it was found that the package condition was the most significant factor among other characteristics (Table 3). One sample was excluded due to insufficient information for registration verification. Counterfeit medicines were 20 times more likely to be found among medicines from open containers/packs than medicines from intact containers/packs (odds ratio: 20.41, $P<0.05$). Registration status became the second most significant influential factor in predicting counterfeit medicine (odds ratio: 6.24, $P<0.05$).

Pharmaceutical Quality

Among 679 samples, 31 (4.6%) failed in HPLC tests for active ingredients, and among 476 samples, 40 (8.4%) failed in solubility tests. Statistically significant association correlated samples that failed in their content analyses and samples failed for solubility tests (Fisher's exact test, $P<0.001$). Logistic models for the analysis of contents of 487 samples predicted that medicines that failed in their content analysis are 12 times more likely to be counterfeit medicines then authentic medicines, and are more available in rural areas and/or from non-licensed outlets (Fisher's exact test, $P<0.05$) (Table 4).

DISCUSSION

According to a recent report, only 30% of the demand for pharmaceutical products in Cambodia is being met by the domestic product, and more than 130 companies are exporting to and distributing medicines in Cambodia (10). However, weak implementation of regulation, poverty, illiteracy and lack of consumer awareness increases the spread of counterfeit medicine.

Table 2 Characteristics of the Counterfeit Medicines Identified

Sl.	Year	Active ingredient	Strength	Dose form	Labeled origin	Package	Shop Category	Registration status in Cambodia	Area of collection	HPLC
1	2006	Paracetamol	500 mg	Tablet	India	Intact pack	Non-licensed	Registered	Urban	Passed
2	2007	Amoxicillin	250 mg	Tablet	Malaysia	Loose medicine	Pharmacy	Registered	Urban	Passed
3	2007	Amoxicillin	250 mg	Tablet	Malaysia	Open container	Non-licensed	Registered	Urban	Passed
4	2007	Amoxicillin	500 mg	Capsule	China	Open pack	Non-licensed	Not registered	Urban	Failed
5	2007	Amoxicillin	500 mg	Capsule	China	Open pack	Pharmacy	Not registered	Rural	Failed
6	2007	Ampicillin	500 mg	Capsule	China	Open pack	Pharmacy	Not registered	Rural	Failed
7	2007	Ampicillin	500 mg	Capsule	China	Open pack	Depot B	Not registered	Rural	Failed
8	2007	Paracetamol	500 mg	Tablet	Hong Kong	Open container	Non-licensed	Not registered	Rural	Passed
9	2008	Albendazole	400 mg	Tablet	United Kingdom	Loose medicine	Non-licensed	Not registered	Urban	Not done at NHQC, but failed at manufacturer's analysis
10	2008	Mebendazole	500 mg	Tablet	India	Open container	Depot B	Not registered	Rural	Passed
11	2008	Mebendazole	500 mg	Tablet	India	Open container	Depot B	Not registered	Rural	Passed
12	2008	Mebendazole	500 mg	Tablet	India	Open container	Depot B	Not registered	Rural	Passed
13	2008	Mebendazole	500 mg	Tablet	India	Open container	Depot B	Not registered	Rural	Passed
14	2008	Mebendazole	500 mg	Tablet	India	Open container	Non-licensed	Not registered	Rural	Passed
15	2008	Metronidazole	250 mg	Tablet	Cambodia	Loose medicine	Depot A	Registered	Urban	Passed

Table 3 Logistic Analysis of Authenticity Investigation Against Influential Factors

N = 512	Authenticity		Odds Ratio (95%CI)	
Factors	Authentic	Counterfeit	Adjusted	Not Adjusted
Package condition				
Intact container/pack	291	1	1.0	
Open container/pack	206	14	20.41(2.55–163.49)	19.78(2.58–151.58)
Registration Status				
Registered	369	4	1.0	
Not registered	128	11	6.24(1.77–22.05)	7.99(2.48–25.34)
Origin				
Domestic	214	1	1.0	
Foreign	283	14	4.7(0.54–40.83)	10.59(1.38–81.13)
Category of Drug Outlets				
Licensed	374	9	1.0	
Non-licensed	123	6	2.54(0.80–8.10)	2.03(0.71–5.81)
Area				
Urban	251	6	1.0	
Rural	246	9	1.67(0.54–5.14)	1.53(0.54–4.36)

Our data suggest that non-licensed outlets have been gradually disappearing, especially in the capital, either due to closure or accreditation, indicating a strengthening of regulatory efforts (11). However, most of the Pharmacies were run by staff who were not pharmacists (7,15–17). To make them an efficient work force, basic orientation and refresher training could be implemented. Enforcement of licensing system could be extended to the peripheral parts of the country to cover all the rural areas.

One of the limitations of the methodology this study could be the dependence on the responses of the manufacturers and MRAs. However, the trends in the response rates yielded in

Table 4 Logistic Analysis of Assay Against Influential Factors

N = 487	Content		Odds Ratio (95%CI)	
Factors	Pass	Fail	Adjusted	Not Adjusted
Authenticity				
Authentic	458	15	1.0	
Counterfeit	10	4	11.91(2.47–57.55)	12.21(3.44–43.42)
Package condition				
Intact container/pack	274	9	1.0	
Open container/pack	194	10	1.23(0.44–3.44)	1.57(0.63–3.93)
Registration Status				
Registered	340	13	1.0	
Not registered	128	6	0.69(0.21–2.30)	1.23(0.46–3.29)
Origin				
Domestic	198	7	1.0	
Foreign	270	12	1.10(0.39–3.11)	1.26(0.49–3.25)
Category of Drug Outlets				
Licensed	354	10	1.0	
Non-licensed	114	9	2.43(0.92–6.36)	2.8(1.11–7.05)
Area				
Urban	243	5	1.0	
Rural	225	14	2.77(0.93–8.24)	3.02(1.07–8.53)

this study indicate that it is possible to increase cooperation from the stakeholders. Increasing manufacturer involvement in the regulatory process may be an effective method of regulation, because the manufacturers might be the right authority to comment on their products.

From the packaging status of the counterfeit samples, it was evident that some of the containers/packs could have been tampered with at the pharmacy or at the retail shops. Several of the samples were mixed together in one pack/container, which illustrates the need to improve and standardize pharmacy practices in the country. The second most prominent characteristic of the counterfeit medicines is that most of them did not have registration, which very clearly indicates failure to prevent intrusion of unregistered items in the circulation. In these circumstances, there is a strong need to build awareness on the issues of counterfeit medicines among the health professionals working in the drug outlets.

Logistic regression suggests that the counterfeit medicines were more likely to fail in the content analysis, similar to other reports (12,13). By putting some false or actual ingredients in fake drugs, counterfeiters may try to trick customers, as patients may think that they are getting better and recovering from their illness. Future research on practices at different stages in the pharmaceutical supply chain could generate more information for the policy makers.

CONCLUSIONS

From the findings of this study it is evident that there are counterfeit medicines among commonly used lifesaving medicines, such as antibiotics, analgesics and anti-parasitics available in the community drug outlets of Cambodia. These counterfeit medicines were more likely to be among medicines with open containers/packs and/or having no registration. Counterfeit medicines were commonly substandard in nature. To safeguard the medicinal supply chain from the intrusion of counterfeit medicines, it is critical to increase awareness in the community and the training of the community medicine sellers. Authenticity investigations might be the most practical and cost-effective approach for developing countries to detect counterfeit medicines.

ACKNOWLEDGEMENTS

This survey received financial support from the Japan Pharmaceutical Manufacturers Association (JPMA). We sincerely acknowledge the cooperation received from the Department of Drugs and Food, Ministry of Health, Cambodia. We are grateful to the Medicine Regulatory Authorities of the manufacturing countries and all of the manufacturers of the samples for their generous cooperation. Additionally, MHK thanks Mr. Ismail Md. Mofizur Rahman for his valuable suggestions and cooperation in preparing this manuscript.

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