Medicine Quality Monitoring in Cambodia

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Introduction

Poor medicine quality is one of the factors contributing to the growing resistance of infectious diseases to pharmaceutical interventions. Counterfeit and substandard medicines can lead not only to protracted illness or adverse drug events, but can also contribute to the emergence of multi-drug resistant infectious pathogens. In Southeast Asia, this is of great concern due to the emergence of drug-resistant malaria, tuberculosis, and HIV as well as outbreaks of H1N1 and H5N1 flu strains.

The Ministry of Health of Cambodia, with technical assistance provided by the Drug Quality and Information Program (DQI)—a project funded by the U.S. Agency for International Development (USAID) and the Global Fund to Fight AIDS, Tuberculosis and Malaria—implemented by the United States Pharmacopeia, has taken action since 2003 to improve the quality of medicines used in priority disease programs in the Mekong.

In close collaboration with the World Health Organization (WHO) Mekong Malaria Programme and the National Malaria Control Programs, DQI has been working to strengthen medicine quality control systems in Cambodia, Laos, Thailand, Vietnam, and Yunnan Province of China. Evidence suggests that the trade in counterfeit medicines is widespread in Southeast Asia and presents a great threat to the lives of patients, especially in rural Mekong countries.

Methods

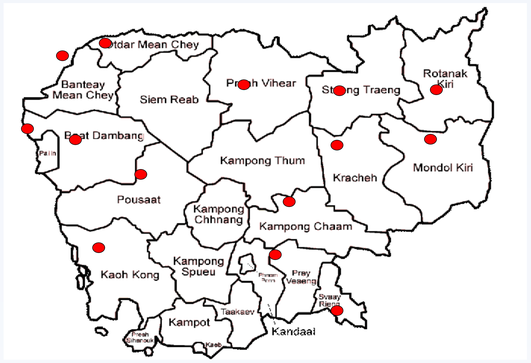

Figure 1. Cambodian provincial sites equipped with the Minilab®

The National Malaria Programme (CNM) and the Department of Drugs and Food (DDF) have been collecting and testing medicines in the public and private sectors in Cambodia since 2003. The project began with antimalarial medicines and eventually expanded to include quality monitoring of anti-tuberculosis, antiretroviral, antiviral, and antibiotic medicines. Medicine quality monitoring is now conducted in thirteen provincial sites using the Global Pharma Health Fund (GPHF) Minilab® for basic testing. Inspectors from the provincial health departments equipped with Minilabs® regularly collect medicines from legal and illegal pharmaceutical outlets and drug stores, sampling the drug classes mentioned above (known as 'postmarketing surveillance').

Methods

After completing a detailed sample collection form, inspectors screen the medicines for quality defects. The samples are analyzed using three basic field screening tests according to protocols developed by the GPHF and DQI:

1. Visual and physical inspection
2. Simple disintegration
3. Thin Layer Chromatography (TLC)

Samples that fail are sent, along with a random selection of 'passed' samples to ensure QA of testing, to the National Health Products Quality Control Centers (NHQC, formerly the NLDQC) in Phnom Penh for verification testing. Tests are conducted according to pharmacopeial monographs for each medicine preparation. Failed samples are considered to be either 'substandard' or 'counterfeit' according to Cambodian pharmaceutical legislation.

Results

Since 2003, a total of 1,247 infectious diseases medicines have been sampled during seven rounds of routine medicine quality monitoring, of which 76 samples failed quality testing. An additional 334 anti-malarial medicines were sampled during a focused, randomized study according to protocol in 6 provinces along the Thai-Cambodian border during 2009, of which 46 samples failed quality testing.

	total samples	total failed samples	% fail
Round 1	**102**	**8**	**7.8**
Round 2	**83**	**11**	**13.3**
Round 3	**80**	**5**	**6.3**
Round 4	**185**	**23**	**12.4**
Round 5	**242**	**5**	**2.1**
Round 6	**246**	**9**	**3.7**
Round 7	**309**	**15**	**4.9**

For routine monitoring, the products that failed were antimalarial and antibiotic medicines:

Failed products	# failed
CHLOROQUINE	**16**
CHLORAMPHENICOL	**8**
ARTESUNATE	**5**
QUININE	**6**
TETRACYCLINE	**6**
DIHYDROARTEMISININ	**1**
AMOXICILLIN	**11**
AMPICILLIN	**10**
ERYTHROMYCIN	**3**
PENICILLIN V	**10**

Results

Testing of antimalarial medicine samples from the Thailand-Cambodia border study resulted in the following failed products:

Name of Sample	Reasons of failure	No. of samples
ARS	Assay: API (86.96%) [ref. 90.0-110.0%]	1
	Assay: API (88.3%) [ref. 90.0-110.0%] + Related subs: >2% [ref. NMT 2%]	1
	Assay: API (0%) [ref. 90.0-110.0%] + Disinteg.> 1h [ref. LT 30mn]	3
	Dissol..: < 60% [ref. NLT 60% in 30mn] + Related subs > 2% [ref. NMT 2%]	1
	Related subs: > 2% [ref. NMT 2%]	9
ARS +MEQ	Assay: ARS API (77.7%) [ref. 90.0-110.0%] + Impurities in ARS > 2% [ref. NMT 2%] in Malarine	2
ARMN/PIP	Assay: ARMN:30.4mg/tab (48.6%) + PIP:189.1mg/Tab (50.4%) [ref. 90.0-110.0%] (Artequick)	1
	Assay: ARMN:29.8mg/tab (4.8%) + PIP:190.2mg/Tab (50.7%) [ref. 90.0-110.0%] (Artequick)	1
DHA	Assay: (87%) [ref. 90.0-110.0%] (Cotecxin)	1
DHA/PIP	Dissol.: DHA: 1.9-31.7mg (4.7-79.2%) *PIP: 2.6-308.8mg (0.8-96.5%) (Duo-cotecxin)	1
	Dissol.: DHA: 0mg *PIP 0mg (0%) [NLT 75%]	5
	Dissol.: 0- 33 mg DHA + 0- 298.6 mg Pip phosphate in 45 mn (Duo-cotecxin)	2
	Dissol.: DHA: 0.8-29.3mg (2-73.2%) *PIP: 1.6-317.4mg (0.5- 99.1%) (Duo-cotecxin)	1
CHLQ PHOSP	Dissol.: < 75% [ref. NLT 75% in 45mn]	1
	Disinteg. > 1h [ref. NMT 60mn]	6
TETRA	Dissol.: 1.04%-13.8% [ref. NLT 80% in 60mn]	3
	Dissol.: 25.3% -35.2% [ref. NLT 80% in 60mn]	1
	Disinteg.: > 60mn [ref. NMT 60mn]	1
QUIN S	No API: (0.0%) - Quinine sulphate	5
	Total	**46**

Legend: ARS – Artessunate; CHLQ HCL – Chloroquine hydrochloride; CHLQ PHOSP– Chloroquine phosphate; DHA- Dihydroartemisinin; DOXI – Doxicycline; MEQ – Mefloquine phosphate; PIP- Piperaquine; QUIN 2HCl – Quinine dihydrochloride ; QUIN S – Quinine sulfate ; S/P – Sulfadoxine/Pyrimethamine; TETRA – Tetracycline hydrochloride

Frequently, medicines that failed were products of 'ghost manufacturers' which, despite label claims on the packaging, do not actually exist. During routine medicine quality monitoring, the following 'claimed manufacturers' were among the most commonly discovered counterfeits:

- VKP Pharmaceutical Co Ltd Thailand
- Shen Wei Pharmaceutical Co Ltd China
- China Southern Dha Zong Pharmaceutical Co Ltd
- Shijazhang Ouyi Pharmaceutical Co Ltd
- Fu Li Pharmaceutical China

Examples of counterfeit products detected during medicine quality monitoring in Cambodia are pictured.

Results

Conclusions

Steps taken to address the issue of substandard and counterfeit medicines include regular meetings of the central level Interministerial Committee on Counterfeit Drugs to determine enforcement actions to be implemented by the Department of Drugs and Food. Additionally, public awareness campaigns educate consumers on the existence and types of counterfeit medicines circulating in the market, via brochures, articles, and circulars produced by the Pharmacists' Association of Cambodia and the DDF. Product recalls and importation bans are important actions taken meant to remove substandard and counterfeit products from Cambodia.

Medicine quality monitoring through low-cost, effective screening in the field is a crucial component for ensuring high quality products.

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