

Cambodian Ministry of Health Takes Decisive Actions in the Fight Against Substandard and Counterfeit Medicines

Laura A Krech^{1*}, Christi Lane-Barlow¹, Lang Siv¹, Souly Phanouvong¹, Wei Elaine Yuan¹, Bunkiet Heng², Dararath Eav², Sovannarith Tey³ and Lukas Roth¹

¹Promoting the Quality of Medicines Program, Global Health Impact Programs, United States Pharmacopeial Convention, USA

²Department of Drugs and Food, Ministry of Health of Cambodia, Cambodia

³National Health Product Quality Control Center, Ministry of Health of Cambodia, Cambodia

Abstract

Cambodia's Ministry of Health and the Department of Drugs and Food have been actively working to reduce the amount of poor quality medicines circulating in the pharmaceutical sector since fake mefloquine and artesunate were first found in 1998. From 2005-2012, legal private sector facilities and illegal outlets in twelve Cambodian provinces were targeted for routine surveillance of medicine quality through sample collection and testing of various anti-infective medicines, the majority of which were anti-malarials and anti-biotics. The Medicine Quality Monitoring program samples from the field were analyzed through a three level approach including field and advanced laboratory testing. 4,381 medicines were collected and tested from 2005-2012; 106 have failed quality testing resulting in an overall failure rate of 2.4%. 28 of the failed samples (26.4%) were counterfeit. The most commonly found counterfeit medicines were chloroquine, artesunate, mefloquine, ampicillin and penicillin. Cambodia has closed over 99% of illegal pharmacy outlets through the Inter-Ministerial Committee to Fight against Counterfeit & Substandard Medicines (IMC) by the end of November 2011. In the past, a lack of resources as well as coordination among the various ministries was identified as a major barrier in combating the presence of poor quality medicines. With financial support from USAID, PMI, and other donors, paired with the technical support from the U.S. Pharmacopeial Convention Promoting the Quality of Medicines program, the IMC developed an action plan to significantly reduce the number of substandard and counterfeit medicines. Based on the data shown, the plan has been successful in reducing the failure rates of samples collected in Cambodia from a high of 7.4% in 2006 to a low of 0.7% in 2011. Continued efforts to monitor and actively ensure the quality of medicines in Cambodia will be required to maintain these low rates; sustainability of these efforts is critical.

Keywords: Drug resistance; Anti-biotics; Medicines

Introduction

As one of the first locations in South-East (SE) Asia to identify counterfeit malaria medicines, Cambodia has been working to reduce poor quality medicines since counterfeit mefloquine and artesunate were first noticed in 1998 [1]. The World Health Organization (WHO), in partnership with member countries and other organizations, lists medicines that have any sort of quality problem as substandard/spurious/false-labelled/falsified/counterfeit (SSFFC) medical products. For brevity, this article will use the term "poor quality" to cover all SSFFC medicines in general [2].

The use of poor quality medicines may lead to treatment failure, increased morbidity and mortality, and the development of drug resistance [2,3]. The border area between Cambodia and Thailand has a history of malaria parasites resistant to a number of therapeutic agents [2-5]. Beginning in the 1960s, malaria in this region first became resistant to chloroquine followed by sulfadoxine-pyrimethamine [6,7]. These resistant parasites then spread to the rest of the world, rendering these key chemotherapeutic agents essentially ineffective in treating malaria [8].

Recently, artemisinin resistant *Plasmodium falciparum* malaria has been documented [9-13]. Convenience sampling [i.e. opportunity sample; not-randomized] in mainland SE Asia in 2000/2001 and 2002/2003 showed that 38% and 53%, respectively, of artesunate obtained from pharmacies and shops were counterfeit [14-18]. A study in 2006 in Cambodia demonstrated that 72% of quinine, 20% of artesunate, 27% of tetracycline, 9% of chloroquine, and 8% of mefloquine samples failed medicine quality testing [19]. Counterfeit quinine and tetracycline found was labeled as made by the "Brainy

Pharmaceutical Limited Partnership," which is not registered in either Thailand or Cambodia. Previous investigations in the region have revealed production and circulation of counterfeit antimalarials (AMLs), generating concern and spurring targeted research in this area [20]. In 2009, a baseline study of the quality of AMLs conducted in 6 provinces in Cambodia showed an overall failure rate of 12.3%, and an alarming 86.2% of the 1,912 households surveyed had a family member who had suffered from malaria in the previous year [21].

The lack of sufficient human and financial resources to assert effective market-access control and monitoring, paired with the limited knowledge of the consuming public and a tendency to purchase cheaper products of unknown quality contribute to the increased prevalence of poor quality medicines in developing countries [19]. This unfortunately, also largely describes the situation in Cambodia.

Since 2003, the Drug Quality and Information (DQI) program and the Promoting the Quality of Medicines (PQM) program—initiated in 2009 to further expand the DQI program—have been providing

***Corresponding author:** Promoting the Quality of Medicines Program, Global Health Impact Programs, United States Pharmacopeial Convention, Twinbrook Parkway 12601, Rockville, MD 20852-1790, USA, Tel: 240-221-4100; E-mail: krechla@aya.yale.edu

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technical assistance to support post-marketing surveillance to the Cambodian Ministry of Health's Department of Drugs and Food (DDF); the National Health Products Quality Control Center (NHQC); the National Center for Malariology, Parasitology, and Entomology (CNM); and other National Disease Program (NDP) centers in an effort to assist in strengthening medicines quality assurance and quality control (QA/QC) systems in Cambodia. Both DQI and PQM were/are implemented by the U.S. Pharmacopeial Convention (USP) with financial support from the U.S. Agency for International Development (USAID); the President's Malaria Initiative (PMI) also provides funding for PQM activities related to malaria in the region.

Cambodia has established the Inter-Ministerial Committee to Fight against Counterfeit & Substandard Medicines (IMC). The IMC consists of Cambodia's Ministries of Agriculture; Commerce; Economy and Finance; Education, Youth and Sport; Forestry and Fisheries; Health; Information; Interior; and Justice. The IMC developed an action plan to significantly reduce the number of substandard and counterfeit medicines and has actively implemented it over the past few years.

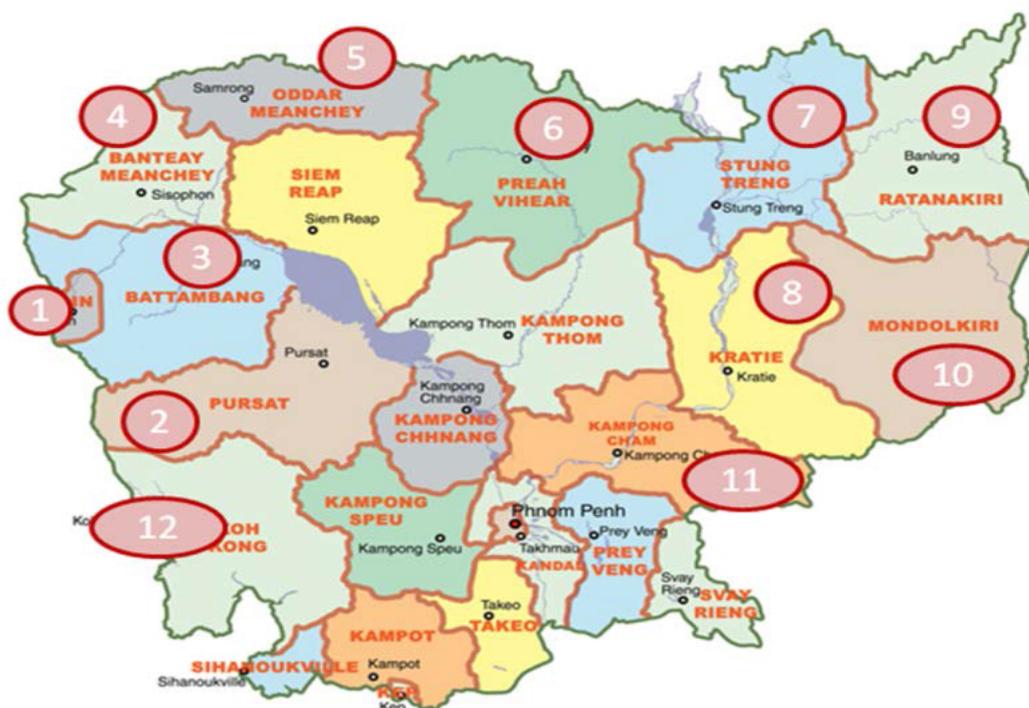
From January 2009 through October 2011, led by the World Health Organization in co-operation with the Cambodian Ministry of Health, a large-scale containment project for artemisinin-resistant *Plasmodium falciparum* malaria was initiated to examine and limit the

spread of resistance. Poor quality antimalarials are believed to allow malaria parasites to become resistant to treatment [22,23]. A portion of this Bill and Melinda Gates Foundation-funded effort was to determine the prevalence of poor quality antimalarials in both the public and private health sectors of Cambodia. Following the evidence identified through this project, pressure has been brought to contain resistance to in certain areas on the Thai-Cambodia border [21]. The data presented in this paper identifies the impact on the prevalence of poor quality medicines, which has occurred prior to, and following the initiation of the containment project.

Methods

From 2005-2012, private sector health facilities in the 12 provinces with sentinel sites shown in Figure 1 were targeted for sample collection from the medicine classes shown in Table 1. Sentinel sites are areas within the provinces where the DDF/MOH have staff and offices and collaborate with the PQM program. Throughout the 12 provinces, provincial, and district level staff acted like regular customers and purchased multiple medicines in their original dispensing packages.

In Cambodia, most medicines were collected from various retail outlets in the private and informal sectors. The private sector consists of licensed establishments that dispense and/or commercialize



1. Pailin
2. Pursat
3. Battambang
4. Banteay Meanchey
5. Oddar Meanchey
6. Preah Vihear
7. Strung Treng
8. Kratie
9. Ratanakiri
10. Mondolkiri
11. Kampong Cham
12. Koh Kong

Figure 1: Location of Sentinel Sites in Cambodia.

Drugs for the Treatment of Tuberculosis	Anti-inflammatory and Anti-rheumatic Products, Non-Steroids
Rifampicin	Ibuprofen
Levofloxacin	
	Anti-virals for the Treatment of HIV Infections
Anti-mycotics for Systemic Use	Stavudine
Fluconazole	Nevirapine
	Lamivudine
Anti-histamines for Systemic Use	
Cetirizine	Anti Malarials
Levocetirizine	Artesunate
	Chloroquine
Anti-bacterials for Systemic Use	Quinine
Amoxicillin	Tetracycline
Ampicillin	Mefloquine
Azithromycin	
Chloramphenicol	
Ciprofloxacin	
Cloxacillin	
Erythromycin	
Penicillin	

The vast majority of medicines sampled were anti-bacterials for systemic use and anti-malarials

Table 1: Therapeutic Classes /Types of Medicines Sampled’.

medicines independent of government health programs. The informal sector consists of unregulated establishments and vendors that operate without a license to sell medicines. The public sector was not included in this program; this sector consists of institutions under the direct control of the Ministry of Health, other governmental institutions, or faith based organizations.

As stated above, field research and data have shown that poor quality medicines have a greater likelihood of being found in markets, as well as cross-border and rural areas within the public, private and informal sectors [16,17,19,21]. The focus of the Cambodia PQM program discussed in this paper is the private and informal sectors only.

In addition to the routine Medicines Quality Monitoring (MQM) at the 12 sentinel sites, in 2010 and 2012, two special investigations were carried out by teams of inspectors from the DDF/MOH and the IMC, in collaboration with PQM, in Cambodian provinces where medicines had not previously been collected and tested. Selected antibiotics were randomly collected and tested, and where specific concerns were identified to the inspectors, suspect products were also taken for quality testing. The results of these special investigations are also included here.

Samples from the field are analyzed through a three level approach [24]. Level 1 analysis includes visual inspection of the package and label and physical inspection of the product. At the sentinel site level, Global Pharma Health Fund (GPHF) Minilabs’ are used for Level 2 testing to determine identity, content, impurities and disintegration [25]. Thin-layer chromatography (TLC) is performed via comparisons to secondary reference standards for the active pharmaceutical ingredients of interest; in addition, data documentation and reporting of Level 1 and 2 testing results are completed. Samples that fail, or are borderline, as well as a 10% random subset of the samples that pass, are further verified through Level 3 analyses (for example, HPLC and dissolution) that require the assessment of all critical quality attributes

based upon the pharmacopeia utilized. In most cases the United States Pharmacopeia was used; for other medicines where no USP monograph was available, the International Pharmacopeia, the Pharmacopeia of the People’s Republic of China and/or in house validated analytic methods were used. Qualities testing of all medicines were performed at the National Health Product Quality Control Center in Phnom Penh.

Results

The DDF and local authorities, working together with PQM, have consistently found counterfeit and substandard (CSM) antimalarial and antibiotic medicines among those sampled. Figure 2 illustrates the declining failure rate from a high of 7.4% of samples in 2006 to a low of 0.7% in 2011. The total number of medicines collected and tested during this time was 4,381; out of this total, 106 failed quality testing, resulting in an overall failure rate of 2.4%.

When comparing the period prior to 2009 with the period from 2009 onward there is a statistically significant reduction ($p=0.0065$) in the failure rate of 3.8% in 2005-2008 [33/877 samples failed, 95%CI 2.7, 5.2] and the failure rate of 2.1% for the period from 2009-2012, [73/3484 samples failed, 95%CI 1.7, 2.6]. Over this time frame, samples were collected from a varied panel of outlets, increasing the chance that poor quality medicines would be located (Table 2).

As seen below in Table 3, provincially, there is a high level of variability in the prevalence of poor quality medicines. The highest rate of medicines that failed quality testing was in Phnom Penh, where there is the largest number of pharmacy outlets and market for pharmaceuticals in Cambodia. In addition this rate was quite high because products that were already suspected and/or reported to be of poor quality were purposely targeted. The rate in Phnom Penh is nearly twice as high than that in Prey Veng, a peri-urban area south of Phnom Penh along the main highway to Ho Chi Minh City in neighboring Vietnam. Several provinces are clustered in the 3%-6% range. Medicines were collected in the provinces of Mondulkiri, Kampong Thom, Kampot and Kandal, but no failures were reported.

Counterfeit medicines

Counterfeit medicines have been consistently found each year from 2003-2012 through PQM’s MQM program; MQM is part of the MOH/DDF’s post-marketing surveillance for all medicines. A counterfeit medicine by Cambodia’s legal definition is a product that [26]

- Is deliberately produced with an incorrect quantity of active ingredient, or wrong active ingredients
- Is without an active ingredient/s, or with an amount active ingredient/s that are deliberately outside the accepted standards (higher or lower) as defined in standard pharmacopoeias
- Is deliberately and fraudulently mislabeled with respect to identity and/or source
- Has fake packaging or is repackaged or produced by any unauthorized person.

Medicines also continue to fail compendial quality testing due to inadequate or excessive amounts of active pharmaceutical ingredients, high levels of impurities, and failure of dissolution testing.

In Table 4 below, the greatest number of counterfeit medicines was found in 2009. A total of 28 counterfeit medicines were found from 2005-2009, however it is important to note that 21 counterfeits

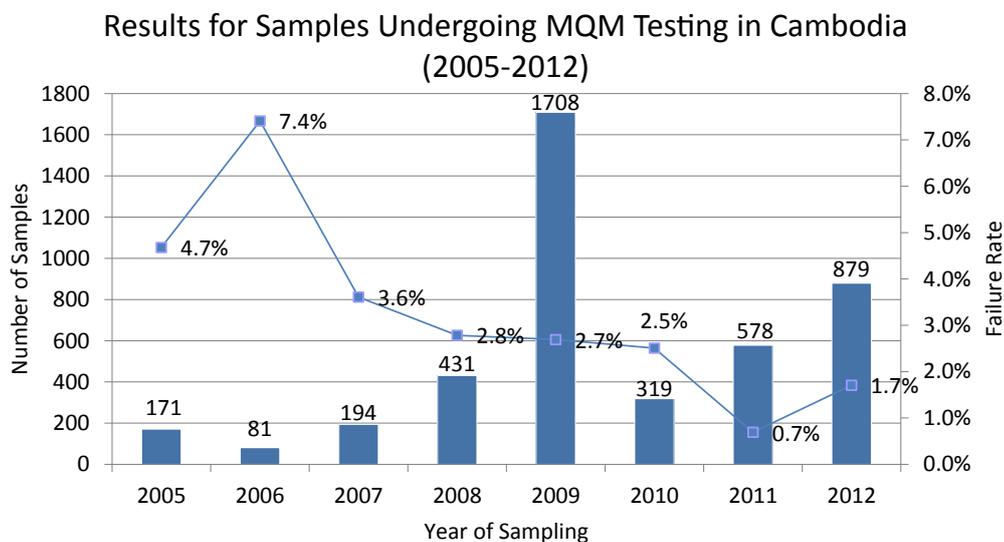


Figure 2: Failure Rates of Sampled Medicines by Year.

API	Fail	Pass*	Total	% Failed**
Amoxicillin	24	443	467	5.1%
Chloroquine	15	334	349	4.3%
Ampicillin	12	394	406	3.0%
Chloramphenicol	6	256	262	2.3%
Artesunate	5	195	200	2.5%
Cloxacillin	5	104	109	4.6%
Penicillin V (Phenoxymethylpenicillin)	5	110	115	4.3%
Azithromycin	4	8	12	33.3%
Levocetirizine	4	18	22	18.2%
Tetracycline	4	723	727	0.6%
Cetirizine	3	18	21	14.3%
Erythromycin	3	82	85	3.5%
Ibuprofen	3	17	20	15.0%
Penicillin G (Benzylpenicillin)	3	18	21	14.3%
Levofloxacin	2	18	20	10.0%
Mefloquine	2	13	15	13.3%
Ciprofloxacin	1	280	281	0.4%
Fluconazole	1	19	20	5.0%
Quinine	1	17	18	5.6%
Rifampicin	1	34	35	2.9%
Stavudine, Lamivudine, Nevirapine	1	6	7	14.3%
Ampicillin/Cloxacillin	1	0	1	100.0%
Grand Total (including all APIs collected/tested)	106	4255	4361	2.4%

Note: This table is not an exhaustive list of all medicines sampled and tested; rather it highlights the APIs that failed quality testing.

*Passed: a sample passed when it conformed with specifications of identification, content of active pharmaceutical ingredient(s), and met other quality attributes, e.g., disintegration and dissolution or impurities.

**Failed means either one or more of the above was not met.

Table 2: Failure Rate (%) by Active Pharmaceutical Ingredient (API) in Cambodia 2005-2012.

were found in 2009 alone. From 2010-2012, 27 medicines were found that failed quality testing and were considered to be of poor quality; however, no counterfeit medicines were found.

Out of the 106 total medicines that failed quality testing, 28 (26.4%) were counterfeit as defined under Cambodian law.

Actions taken by the Cambodian Ministry of Health included: (1) An official declaration banning these particular counterfeit versions of these medicines. The official declaration listed the name of the product,

the manufacturer, and country of origin as listed on the packaging. (2) These products were withdrawn by the MOH in private sector establishments. (3) A television announcement was broadcasted and a leaflet with the counterfeit product/manufacturer information was heavily circulated to health professionals as well as the public.

Figure 3 illustrates the country source of poor quality medicines for the 106 failed samples identified between 2005 and 2012. Based on the information written on the product packaging, India was the source

Province	Fail	Pass	Total	% Failed
BanteayMeanchey	12	396	408	2.9%
Battambang	10	331	341	2.9%
Kampong Cham	7	398	405	1.7%
Kampong Speu	2	29	31	6.5%
Kampong Thom	0	28	28	0.0%
Kampot	0	33	33	0.0%
Kandal	0	18	18	0.0%
Koh Kong	3	407	410	0.7%
Kratie	6	232	238	2.5%
Mondulkiri	0	210	210	0.0%
OddarMeanchey	3	264	267	1.1%
Pailin	8	329	337	2.4%
Phnom Penh	6	22	28	21.4%
PreahVihear	22	358	380	5.8%
Prey Veng	4	28	32	12.5%
Pursat	6	406	412	1.5%
Ratanakiri	6	372	378	1.6%
Siem Reap	1	14	15	6.7%
SteungTreng	6	257	263	2.3%
SvayRieng	2	87	89	2.2%
Takeo	2	31	33	6.1%
Unknown	0	5	5	0.0%
Grand Total	106	4255	4361	2.4%

Table 3: Failure Rate % of Medicines Sampled in Cambodia by Province (2005-2012).

for 32% of failed samples, China 20%, Thailand 19%. Locally produced Cambodian products accounted for 14% of poor quality medicines.

Discussion

Since the initiation of PQM's collaboration with DDF/MOH, the IMC, and international partners (including WHO, the French Foreign Affairs' *Fonds de Solidarité Prioritaire*, INTERPOL, and Global Fund), there has been a significant decrease in the presence of poor quality antimalarials and antibiotics in Cambodia. While 106 poor quality medicines have been identified since 2005, the majority are not counterfeit medicines, and may be the result of lack of quality manufacturing and supply chain management, transport and storage procedures which result in degradation of active ingredient content.

Resistance is a major concern with both antibiotics and antimalarials and poor medicine quality has been linked to the development of resistant bacteria and parasites; therefore, funding priorities for sample collection and testing targeted these two classes of medicines. The newer artemisinin-based anti-malarials are already demonstrating levels of resistance in patients being treated in areas of the Thai-Cambodia cross border region. Other products such as NSAIDs, anti-histamines, and anti-fungals, which were collected and tested, do not have serious resistance problems like antimalarials.

The top three sources of poor quality medicines were imports (as labeled on the packaging) from India, China and Thailand, suggesting there is an opportunity to address poor quality through regulatory intervention and enforcement of importation standards and registration requirements. Concerted efforts by the Cambodian authorities in this regard have been the driving force to reduce these rates.

In 2004, the USPQI program, working together with the Cambodian MOH/DDF, found that 16.2% of antimalarials sampled in four provinces were identified as poor quality, which led to the creation of the IMC in 2005 [9]. Since the nature of counterfeit medicines is

clandestine, and the opportunities for investigators to access medicines of poor quality in the marketplace varies from province to province and medicine to medicine, this high rate prior to commencing and expanding the MQM program in Cambodia further supports the efficacy of the interventions broadly impacting rates of poor quality medicines. Despite variable survey methods and sampling approaches, the trend continues to decline.

Starting in 2006, Phnom Penh and certain key provinces (Kampong Cham, Kampong Thom, Siem Reap and Battambang) have been exemplary in taking concrete actions to follow up from data generated during post-market surveillance; these include closing down illegal drug outlets and educating the public about poor quality medicines. Specific examples include educational art events and contests, television public service announcements, national distribution of leaflets and posters with images of recently found counterfeit medicines and innovative campaigns with taxi drivers playing radio spots to raise public awareness about the deadly combination of counterfeit medicines and treatment of malaria. All of these efforts have contributed to the significant decline in poor quality medicine samples seen over the years.

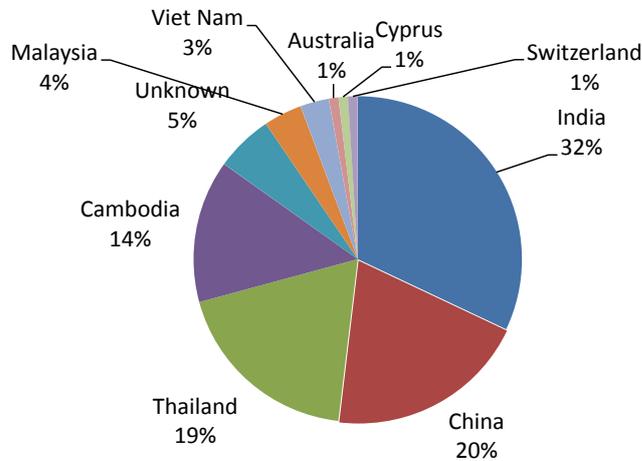
In addition to provincial initiatives, and as a result of PQM MQM activities, the Secretary of State from the MOH released official "Prakas" or bans on the importation or sale of products from specific manufacturers in the country.

Led by the IMC, Cambodia has closed almost all identified illegal medicines outlets. The shops were targeted because of evidence that they were among the primary sources of poor quality medicines in the country.

Year	Province	Active Pharmaceutical Ingredient	Therapeutic Group
2005	Battambang	Artesunate	Antimalarial
	Battambang	Artesunate	Antimalarial
	Pailin	Penicillin	Antibiotic
2006	Battambang	Chloroquine	Antimalarial
	Battambang	Mefloquine	Antimalarial
2007	Battambang	Ampicillin	Antibiotic
2008	Rattanakiri	Chloroquine	Antimalarial
2009	PreahVihear	Amoxicillin	Antibiotic
	PreahVihear	Ampicillin	Antibiotic
	PreahVihear	Ampicillin	Antibiotic
	PreahVihear	Chloroquine	Antimalarial
	Kratie	Chloroquine	Antimalarial
	Kratie	Chloroquine	Antimalarial
	Kratie	Ampicillin	Antibiotic
	Kratie	Amoxicillin	Antibiotic
	Kratie	Amoxicillin	Antibiotic
	Kampong Cham	Chloroquine	Antimalarial
	Kampong Cham	Chloroquine	Antimalarial
	Kampong Cham	Chloroquine	Antimalarial
	Pursat	Chloroquine	Antimalarial
	Rattanakiri	Chloroquine	Antimalarial
	Rattanakiri	Amoxicillin	Antibiotic
	Rattanakiri	Ampicillin	Antibiotic
BanteayMeanchey	Amoxicillin	Antibiotic	

Table 4: Counterfeit Medicines found in Cambodia 2005-2009.

Source of Products with Failed Quality Test 2005-2012: N= 106



Country of Origin of Failed Samples (as claimed on packaging)

Figure 3: Source of Products with Failed Quality Tests Based on the Label Claim.

In December 2012, the Ministry of Health released a statement at the “Workshop on Annual Assessment of the Inter-Ministerial Committee and Provincial Committee for Eliminating of Counterfeit Drugs and Illegal Health Services for Poverty Reduction” that the number of illegal medicines outlets had been reduced from 1420 in 2009 to 87 in 2010, and to almost zero by the end of November 2011.

Limitations

The Cambodia MOH/DDF and PQM only sampled and tested regularly from 12 out of 24 total provinces. There are other areas/provinces that the program could explore, particularly border areas in provinces where no medicine samples are collected and tested. Up until very recently, PQM pooled resources with Global Fund monies to perform medicine quality monitoring and testing. However, delays and cuts in funding have affected activities. In addition the Cambodian government is currently not able to fully fund sample collection and testing, nor able to expand to additional provinces.

It would be interesting to access the public sector; this data only includes private and informal sector data. Public sector medicines have been sampled and tested in previous studies (as cited in the introduction) and are currently being sampled and tested for specific studies. High-level government approval is needed in order to sample from the public sector. This data should not be interpreted as a “snapshot” of the total number of poor quality medicines that are circulating in Cambodia. It is impossible to obtain firm data due to the clandestine nature of the counterfeit medicine trade. The data presented in this paper should be strictly interpreted as reflecting the reality of the specific areas, types of outlets (private and informal sectors), and types of medicines examined.

Conclusion

In the past, a lack of resources as well as coordination among the various ministries was identified as a major barrier in combating the presence of poor quality medicines. With financial support from USAID, PMI, and other donors, paired with the technical support from USP’s PQM program and close collaboration with the Cambodian MOH, the IMC developed an action plan to significantly reduce the

number of substandard and counterfeit medicines. Based on the data shown, the plan has been successful in reducing the failure rates of samples collected in Cambodia from a high of 7.4% in 2006 to a low of 0.7% in 2011. Continued efforts to monitor and actively ensure the quality of medicines in Cambodia will be required to maintain these low rates; sustainability of these efforts is critical.

Regarding the existence of substandard medicines in Cambodia, challenges continue to exist in improving Good Manufacturing Practices (GMP), Good Pharmacy Practices (GPP), and Good Storage and Distribution Practices (GSDP) in pharmacy outlets. Continually increasing awareness of the health impacts of substandard medicines that result from shoddy transport, storage, and handling is needed.

Lastly, as especially observed in 2009, counterfeit medicines still pose a serious threat to the public’s health. The IMC is taking swift and serious actions against importers of counterfeit medicines in Cambodia, however, it is also very important to promptly share as much information as possible about both counterfeit and substandard medicines (photo, lot number, packaging, etc.) with neighboring countries, since the vast majority of medicines that failed quality testing were labeled as originating from China, India, Thailand and Cambodia. Again, the label does not guarantee that the poor quality medicine actually was manufactured from that particular country, but Medicines Regulatory Authorities need to be alerted of these serious quality problems on a timely basis. PQM is looking into collaborations in the near future with WHO and other regional associations such as ASEAN (Association of Southeast Asian Nations) to rapidly circulate counterfeit and substandard medicine information to regulatory authorities in the region.

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