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Antibiotic usage and antimicrobial resistance in indonesia

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Chapter V

Availability and pharmaceutical quality of antibiotics obtained with or without prescription (Over The Counter) in urban Indonesia

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On behalf of the study group "Antimicrobial resistance in Indonesia: Prevalence and
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Submitted

Summary

Background: Our survey of antibiotic use outside hospitals in Indonesia revealed low-dose antibiotic regimens. Despite drug legislation and regulation, 17% of antibiotic users obtained the drugs over the counter (OTC). In the same population, high resistance rates were found.

Objective: To validate the findings of our survey, we investigated the availability and the pharmaceutical quality of active ingredients in frequently used antibiotics.

Methods: In April 2006 a cross sectional study consisting of visits by simulated 'clients' to different medicine outlets was done in a major city on Java. The 'clients' requested a three-day regimen of one of five antibiotics. Samples were photographed, including package and label. The content of the products was analyzed by a certified laboratory and compared with British pharmacopoeia (BP2005) requirements.

Results: In total, 104 products were obtained from 75 pharmacies, 10 drug stores and 39 roadside stalls (kiosks). Pharmacy employees did not refuse or question OTC requests, and no oral or written information was provided. Generic and branded products were dispensed as single blister strips or repackaged in small plastic bags (16%), the latter without the drug name or unit dose. For 95% of samples, the tablets and capsules carried the label made by 14 local manufacturers. The trimethoprim content of 10/20 cotrimoxazole tablets was 20% below BP limits; eight samples carried the label of one manufacturer. The contents of 4/20 amoxicillin and 5/22 tetracycline samples were only <5% below BP limits. There was no association between low content and type of outlet, registration type or packaging. Median retail prices of similar products were invariably higher in kiosks than pharmacies; they varied up to six fold for cotrimoxazole and 20 fold for ciprofloxacin.

Conclusion and recommendations: Our field study confirmed that antibiotics were retailed OTC in pharmacies and kiosks, most often at high prices. The quality in terms of content of cotrimoxazole was substandard and seemed to be related to local manufacturing problems. Enforcement of existing regulations at all types of medicine outlets, better training of pharmacy personnel, control at the national level of antibiotic production by local industries and pricing according to WHO expert reports are strongly recommended.

Key words: Substandard, counterfeit drugs, self-medication, drug content, Asia

Running head: Availability and quality of antibiotics in Indonesia

Introduction

Substandard and counterfeit anti-infective drugs can cause therapy failure through low dosage or absence of active drug, adverse effects through excessive dose or the presence of incorrect or toxic ingredients, and emergence of antimicrobial resistance through subtherapeutic amounts of the antimicrobial drugs [1]. A drug that, upon laboratory testing in accordance with the specifications it claims to comply with, fails to meet the specifications is a substandard drug. Drugs can be substandard among others because they are produced with low quality or chemically instable ingredients or stored under inadequate conditions. According to the WHO definition, a counterfeit drug is one which is deliberately and fraudulently mislabeled with respect to identity, source, or both [2,3]. Counterfeit product can contain the correct amount, too little or too much of the active ingredient. Packaging can provide clues about counterfeiting [4]. The problem of substandard and counterfeit drugs is particularly prevalent in low-income and developing countries. Insufficient regulation and manufacturing control are major causes [2]. In the last decade, substandard anti-malarial, antibacterial and antiviral drugs have been reported in South East Asia [5-8]. In Burma the antibiotic content of 21 products was 13 to 48% lower than indicated [5]. In Laos People's Democratic Republic a significant reduction in low quality tablets or capsules of ampicillin and tetracycline was observed between 1997 and 1999 after implementation of the National Drug Policy program [7]. A recent review in The Lancet stated that most publications did not report the source of counterfeit or substandard drugs and called for reporting the manufacturer's name as stated on the packaging [1].

There are few publications on the quality of anti-infective drugs on the market in Indonesia [9] [10]. Silverman et al. and Lee et al. stated in 1990 [9] and 1991 [11], respectively, that in Indonesia, fraudulent drug products may represent 20-30% of all drug products on the market. However, no methodological details were provided. A strategic report *Indonesia Pharmaceutical and Healthcare Report Q3 2006* also mentioned in 2007 that fake products account for up to 20 % of total drug sales [12]. Drug legislation and regulation do exist in Indonesia. In 2003 the government updated regulations regarding good manufacturing practice for the many local private and state companies that produce medicines, mostly generics [13]. The law categorizes antibiotics

as prescription drugs, to be retailed in pharmacies only [14]. Pharmacies and drug stores need a government license. Pharmacies are allowed to sell all kind of drugs. Drug stores have a limited license and are not allowed to sell antibiotics and narcotics.

We surveyed antibiotic usage in Indonesia [15]. Individuals who visited public healthcare facilities (puskesmas) and who had consumed antibiotics cited short courses (median 3 days) of amoxicillin or ampicillin, chloramphenicol, ciprofloxacin, cotrimoxazole and tetracycline. Similar antibiotics, tetracycline in particular, were self-medicated by 17% of the individuals. Low dosage regimens were reported. Forty-three percent of the individuals carried resistant *Escherichia coli* and 11% *Staphylococcus aureus*, of which 32% were resistant to antibiotics [16]. Antibiotic use was the main determinant for carriage of resistant *E. coli* [17] or *S. aureus* (Lestari ES et al, unpublished data). We hypothesized that the low-dose regimens could have contributed to the development of resistance. In addition, antibiotic tablets or capsules with a substandard content on the market in this area would further expose bacteria to low concentrations in this population. If, on the other hand, some products are counterfeit and contain no antibiotic at all, the conclusions of our studies of the association between use and resistance would be invalid. We investigated the availability and the pharmaceutical quality of the active ingredients of antibiotics frequently used in the outpatient setting in Indonesia. We explored associations of the antibiotic content of samples with a number of variables related to manufacturing and retailing.

Materials and methods

Study design

A cross sectional survey of potential retailers of antibiotics was performed in Surabaya, east Java, in the urban areas surrounding the government hospital and two puskesmas that had participated in our antibiotic survey [15]. Community pharmacies, drug stores, traditional Chinese medicine prescribers (shinshes) or their shops and kiosks (roadside stalls, mostly on wheels (Photograph 1)) were visited. Four volunteers (3 men and 1 woman) were trained to act as clients purchasing antibiotics. They requested the antibiotics with or without prescription by the generic name, as is the custom in

Indonesia. In case they were questioned, they were instructed to cite standard symptoms of infection, e.g. fever, cough, pain while passing urine, etc.

Sample collection

Starting from the government hospital and puskesmas, the four ‘clients’ went in four directions (north, west, south, and east) in the city of Surabaya and visited each retailer on the way in order to purchase 20 samples of five antibiotics (amoxicillin, chloramphenicol, tetracycline, cotrimoxazole, or ciprofloxacin) with or without a prescription. Each retailer was visited once. In Figure 1 the study plan of the sample collection, route and sample size is shown. The following information was recorded: name and address of retailer; type of retailer; obtained with or without prescription; storage conditions of the antibiotic; type of packaging; delivered with or without information leaflet (package insert) or oral instruction, and price.

Analysis of samples

Samples were photographed, including package and information leaflet, if available. Assays of tablets and capsules were performed by Farmalyse (Zaandam, the Netherlands), a certified independent laboratory using high performance liquid chromatography (HPLC) (Thermo Electro Scientific, Breda, the Netherlands). The tests were performed in duplicate. For content assays of cotrimoxazole, tetracycline and chloramphenicol the British Pharmacopoeia BP 2005 monographs and standards were used [18], for ciprofloxacin and amoxicillin the United States Pharmacopeia USP 29 [19].

Statistical analysis

SPSS for Windows version 13 was used for all analyses. Fisher’s exact test was used to analyze the association between substandard quality (using BP limits [18]) and retailer, storage conditions, packaging, manufacturer, whether the product was registered as generic or branded and sold with or without prescription. Prices in pharmacies and kiosks and of generic and branded products were compared by the Wilcoxon signed-rank test.

Results

Medicine outlets and availability of antibiotics

Between 7 and 15 April 2006, the four ‘clients’ requested an antibiotic from the potential medicine retailers in the city of Surabaya along the routes of the study plan. Only one of

the first 10 drug stores and none of the four shinshes/traditional Chinese medicine shops encountered on their routes sold antibiotics. From that moment, samples primarily planned to be purchased in drug stores or from shinshes were requested without prescription in kiosks or pharmacies. The survey covered 15 of the 31 sub-districts in Surabaya; in 12 sub-districts 3-57% of the licensed community pharmacies were sampled. Overall, 12 % of the 655 licensed pharmacies in Surabaya were visited. All but one was private pharmacies and all had air conditioning. Total numbers of drugstores, shinshes, and kiosks in Surabaya were not available, making it impossible to calculate for these retailers the percentage of samples. The requested amount of product was dispensed from boxes (blisters) or bottles of 500 to 1000 units (Photograph 2). All antibiotics and quantities were available in pharmacies, except one pharmacy that dispensed only 17 capsules of chloramphenicol instead of 20. In kiosks, the antibiotics were exposed to sunlight, average high Indonesian temperatures of 32 °C and high humidity (Photograph 1, 3A and B). In six kiosks the requested number of units was not available (4-7 instead of 10 units). Ten kiosks out of 39 did not sell antibiotics.

Antibiotic samples and dispensing

In Table 1 the characteristics of the purchased antibiotics are given. All samples with prescription were acquired from pharmacies. In case of a prescription, pharmacy employees copied dose regimens from the prescriptions onto a slip of paper and attached it to the package. No information leaflets or oral instruction were given. In case of purchases without prescription, the clients were never questioned or referred to a physician. Both in pharmacies and kiosks, products of similar appearance and packaging were dispensed. Most samples were generic products. Twenty-two percent of chloramphenicol, 15% of cotrimoxazole and 60% of tetracycline samples were branded generics. Capsules were repackaged in small plastic bags 16% of which did not have a label with the drug name or unit dose (Photograph 4A and B). For 95% of the samples, the tablets and capsules carried the label made by 14 local manufacturers (Table 2).

Content assay and analysis

Antibiotic samples were collected and stored in an air-conditioned room until transportation for analysis to the Netherlands in the third week of April 2006. According to the BP 2005 criteria, one fifth of amoxicillin tablets and 5 of 22 tetracycline capsules

samples contained slightly less active substance than required (Table 3). Fifty percent of cotrimoxazole tablets had a trimethoprim content which was less than 20% of the required amount. No relationship between substandard content and type of outlet ($p = 0.58$), sold with or without prescription ($p = 0.78$), packaging ($p = 0.8$) or registration type (generic versus branded) ($p = 0.54$) was observed. Substandard antibiotics carried the labels of six manufacturers (Table 2).

Retail prices

In Table 4 a retail price comparison is given, including the price set by the government [20]. Generic products were less costly than branded generic products; for chloramphenicol, cotrimoxazole, and tetracycline the differences were statistically significant. In kiosks, retail prices were significantly higher than in pharmacies. There was no association between retail price and lack of a prescription (data not shown).

Discussion

This field study confirmed that, despite existing regulations, antibiotics could easily be obtained without a prescription from medicine retailers in one of the major cities on Java in 2006. In addition, the content of one-fifth of the antibiotic samples was below pharmacopeial limits. Almost a quarter of the samples of tetracycline and amoxicillin and half of the samples of cotrimoxazole were substandard in terms of content.

The five generic antibiotics were available in all community pharmacies visited. All pharmacies sold the antibiotics OTC. This practice and the lack of appropriate labeling and counseling can partly be explained by the insufficient level of training of pharmacy employees, which does not include information on drugs. Other reasons for insufficient labeling and information could be the practice of repackaging large packaged units. As far as the availability of antibiotics in other medicine outlets that are not licensed for antibiotics is concerned, the situation differed. Drug stores retailed hardly any antibiotics. This was confirmed by a repeat visit to a few drug stores in 2007 (data not given).

Actions of the national Food and Drug Agency might be effective. Distribution and sales of illegally imported drugs is punishable by up to five years of imprisonment and a fine of two billion rupiah (around 218,000 dollars) [21]. In contrast, two-thirds of the kiosks sold small quantities of antibiotics. One of the reasons could be that, having no fixed

address, kiosk owners escape control measures more easily. Although there is no need for kiosks to retail antibiotics for the purpose of availability – for emergencies 24-hour coverage is given by hospital pharmacies, it is clear that kiosks fill a commercial demand. Kiosks are convenient because they are numerous in urban areas, easily accessible and pose no privacy problems for the client with e.g. a sexually transmitted disease. However, consumers may not be aware that resistance against tetracyclines in *Neisseria gonorrhoeae* has approached 100% in urban areas since the nineties [22].

Kiosk owners usually buy their drugs from wholesalers or drug stores. It now seems that, because of recently tightened control of wholesalers and drug stores, kiosk owners obtain the antibiotics from nearby pharmacies and keep a very small stock supply. Therefore, strict enforcement of the law for community pharmacies without controlling the kiosks might make kiosk owners again turn to an alternative illegal supply chain of anti-infectives. Illegal import increases the risk of counterfeit products in other South East Asian countries, [8, 23, 24]. Finally, this study confirms the data of our previous survey [15] and statements in the press [21] that Chinese traditional healers do not retail antibiotics.

The fact that eight of nine cotrimoxazole samples made by one manufacturer according to the label were substandard, out of a total of ten substandard samples, points to a production problem of that manufacturer. For six of the ten substandard products a legible expiry date was printed on the blister package, in all cases beyond January 2008. This makes expiration an unlikely cause of the low content of active ingredient. Although exposure to sunlight, average high temperatures of 32 °C in Indonesia and high humidity could have led to degradation of drugs in kiosks, we found no association of substandard content of the products with the type of medicine outlet.

We cannot prove that the antibiotic samples were produced by the companies printed on the label. However, we have no indication that any of the samples were counterfeit drug products. Packaging and labeling looked identical and all samples contained active ingredients.

In developing countries that struggle with counterfeit drug problems, some samples contained no active ingredient at all or very low amounts [6, 8, 25]. In the present study, apart from cotrimoxazole, deviations from the BP 2005 limits were small. Another recent

study in Indonesia showed a slightly lower content of rifampicin in products from one of three manufacturers [10]. Therefore, we cannot concur with former published statements [9, 11, 12] on fraudulent drugs in Indonesia, although we cannot exclude that the situation has improved recently. The regulations seem to guarantee effectively the presence of genuine antibiotics on the market.

One of the reasons for this study was to exclude the possibility that low drug content might have contributed to the development of the resistance of bacteria against frequently used antibiotics in Indonesia. Although 20% of the antibiotic samples contained lower amounts of antibiotic, it is not likely that, with the exception of trimethoprim, these small deviations would play an important role in the prevalence of resistance. Unjustified use of these antibiotics [15, 26] remains the major avoidable contributor.

Prices of antibiotics with similar labels differed widely, often exceeding the recommended [13] retail prices, except for generic amoxicillin and ciprofloxacin (Table 4). Generic products were less costly than branded products, and prices were lower in pharmacies than kiosks.

This is the first published report in the international literature that provides objective information on OTC sales and the content of frequently used oral antibiotics in Indonesia. The strengths of the study are the large sample size of antibiotics from one stated country of origin and the analysis by a laboratory using validated chromatographic methods.

Because of the *simulated client* method, successfully used for this purpose by others [25] [6] [24], we were able to document real life practices. A more official approach of drug quality assurance assessment including drug pricing according to methods recently developed by WHO [27] and requesting consent of the responsible retailers [28], would not have exposed the OTC sales problem. Limitations of the study are that we were not able to select pharmacies for random sampling [6, 25] [8] [24] because we obtained a list of registered pharmacies in Surabaya only after the sampling was completed. We were not systematically informed about the expiry dates of the samples because this information was missing for the repackaged products or absent from the partial blister strips. However, no legible dates were beyond expiration. We selected the antibiotics based on their substantial usage in the area [26], not on high cost. Therefore, we cannot generalize our findings to all types of antibiotics since expensive antibiotics might be a

more interesting target for counterfeiters. However, large volumes of inexpensive fakes would still provide a worthwhile profit for counterfeiters [1]. We think that our findings are relevant for the urban areas as very similar antibiotic consumption patterns were found in another city on Java [26] and the stated manufacturers were Indonesian companies from different parts of Java which is the main island, containing 59% of the population. Whether the results are true for rural areas or small islands of Indonesia remains to be seen. We analyzed two oral dosage forms only and did not try to study liquid preparations. Our analysis in terms of quality was limited to the content, since we did not perform analyses of impurities or excipients which determine the biological equivalence [19]. We did not perform dissolution tests [29] which would assess the in vitro availability of the drug.

Despite these limitations, we conclude that in OTC retailing of the five most frequently used oral antibiotics was widespread in pharmacies and in kiosks, often at very high prices. Substandard quality of content was limited except for trimethoprim in cotrimoxazole tablets, which most likely was related to local manufacturing problems. Our conclusions on the associations between use and carriers of resistant strains in the area [17] remain valid. We recommend enforcement of existing regulations at all types of medicine outlets, better training of pharmacy personnel, control at the national level of antibiotic production by local industries and pricing according to WHO expert reports [27] [28].

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Conflicts of interest

Not relevant to the content of this manuscript .

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Table 1. Characteristics of antibiotic products purchased by simulated ‘clients’ at private medicine outlets in Surabaya, Indonesia

Antibiotic samples	Amoxicillin 500 mg N = 20 (10 tablets)	Chloramphenicol 250 mg N = 23 (20 capsules ^c)	Ciprofloxacin 500 mg N = 19 (10 tablets)	Cotrimoxazole 480 mg N= 20 (10 tablets)	Tetracycline 250 mg N = 19 (10 capsules)	Tetracycline 500 mg N = 3 (10 capsules)	Total N = 104
Medicine outlet							
pharmacy/ kiosk /drug store	9/11 /0	19/4/0	17/2 /0	20 /0/0	8/10/1	2/1/0	75/28/1
Prescription							
yes/no	5/15	5/18	5/14	6/14	4/15	1 /2	25 /79
Packaging							
blister/plastic bag	20/0	14/9	19/0	20/0	12/7	2 /1	87/17
Registration							
generic/branded generic	20/0	18/5	19/0	17/3	7/12	2 /1	83/21
Price ^a /product range median (IQR) ^b	290-5000 500 (313-700)	150-1000 325 (250-500)	400-8000 850 (500-850)	145-870 223 (200-405)	138-1000 800 (150-900)	300-750 400(300-750)	138-8000 500 (250-800)

^a In rupiah, ^b Interquartile range, ^c one pharmacy dispensed 17 capsules

Table 2. Manufacturer (city of residence) as stated on blisters and/or logos for 104 products and substandard content assay result

Manufactured by (city)	Substandard assay test results/total						Total
	Amoxicillin	Chloramphenicol	Ciprofloxacin	Cotrimoxazole	Tetracycline		
A (Surabaya)	-	-	-	1/1	-		1/1
B (Sidoarjo)	-	-	0/3	-	-		0/3
C (Bogor)	-	-	-	-	3/11		3/11
D (Palembang)	-	-	0/10	-	-		0/10
E (Jakarta ^a)	-	-	-	-	1/1		1/1
F (Bekasi ^a)	-	0/2	-	-	-		0/2
G (Sidoarjo)	-	-	-	0/1	-		0/1
H (Bekasi)	1/4	0/10	0/2	8/9	0/3		10/28
I (Jakarta)	0/1	0/2	0/1	0/3	0/2		0/9
J (Jakarta ^a)	-	0/1	-	-	-		0/1
K (Semarang)	2/14	-	-	0/1	0/2		2/17
L (Jakarta ^a)	-	0/2	-	0/1	-		0/3
M (Bandung)	-	0/4	0/3	0/3	-		0/10
O (Serang)	1/1	-	-	1/1	-		2/2
Unknown	-	0/2 ^b	-	-	1/3 ^c		1/5
Total	4/20	0/23	0/19	10/20	5/22		19/104

^a Head office address, ^b In small plastic bags and no text or logo on white/green capsules, ^c In plastic bags and no text or logo on red and black caps.; red and black caps. “BMF”; yellow and blue capsules “TETRA 500”

Table 3. Antibiotic content of 104 oral products purchased in medicine outlets in Surabaya, Indonesia

Antibiotic	Required active substance (% , min, max)	Number of samples		Content of active substance mg (% of stated dosage) /tablet or capsule		Content too low ^a
		Pharmacy	Kiosk/Drug store	Min	Max	
Amoxicillin 500 mg tablet	92.5 – 110	9	11	457 (91.4)	481 (96.2)	4 (25) ¹
Chloramphenicol 250 mg capsule	95 – 105	19	4	239 (95.6)	260 (104)	0
Ciprofloxacin 500 mg tablet	95 – 105	17	2	481 (96.2)	506 (101.2)	0
Cotrimoxazole 400/80 mg tablet	92.5 – 107.5 92.5 – 107.5	20	0	391 (97.8) 58 (72.5)	411 (102.8) 81 (101.3)	0 10 (50) ²
sulfamethoxazole trimethoprim						
Tetracycline 250 mg capsule	95 – 105	8	10	226 (90.4)	259 (103.6)	5 (23) ³
Tetracycline 500 mg capsule	95 – 105	2	1	503 (100.6)	514 (102.8)	0

^a Compared with pharmacopeial limits [18]

¹ Two were obtained from pharmacies; ² all were obtained from pharmacies; ³ one was obtained from pharmacy

Table 4. Retail price comparison of the antibiotics

Antibiotics	Recommended ^a retail price ^b	Actual retail price ^b per capsule or tablet median (interquartile range)					
		In pharmacies	In kiosks	p-value	Generic	Branded generic	p-value
Amoxicillin 500 mg tablet	403	300 (300-400)	700 (500-1000)	0.00	500 (313-700)	Not available	-
Chloramphenicol 250 mg capsule	237	258 (230-470)	875 (563-1000)	0.00	254 (224-500)	500 (460-875)	0.00
Ciprofloxacin 500 mg tablet	950	850 (500-1000)	5000 (2000-8000)	0.00	850 (500-1000)	Not available	-
Cotrimoxazole 480 mg tablet	205	223 (200-405)	Not available	-	220 (200-260)	850 (200-870)	0.00
Tetracycline 250 mg capsule	125	150 (150-200)	900 (800-1000)	0.00	150 (150-200)	850 (800-1000)	0.00
Tetracycline 500 mg capsule	266	350 (300-400)	750 (750-750)	0.17	350 (300-400)	750 (750-750)	0.17

^a Maximum retail price set by the Minister of Health in March 2006 [20]

^b in rupiah

Legends

Figure 1

Study plan and actual sample collection of antibiotics from private medicine outlets in areas surrounding public healthcare facilities by simulated clients in the city of Surabaya

1a Itineraries in the area surrounding the public hospital Dr. Soetomo

1b Itineraries in the area surrounding the public healthcare center Puskesmas Pucang Sewu

1c Itineraries in the area surrounding the public healthcare center Puskesmas Mojo

Photographs

1. Kiosk (roadside stall on wheels) in the city of Surabaya.
2. Antibiotic sample in a kiosk; A overview and B detail
3. Antibiotics in large packed units (boxes and bottles) on shelves in a community pharmacy
4. Blister strips of antibiotics and repackaged capsules in plastic bags (A and B) sold in kiosks

Fig. 1a

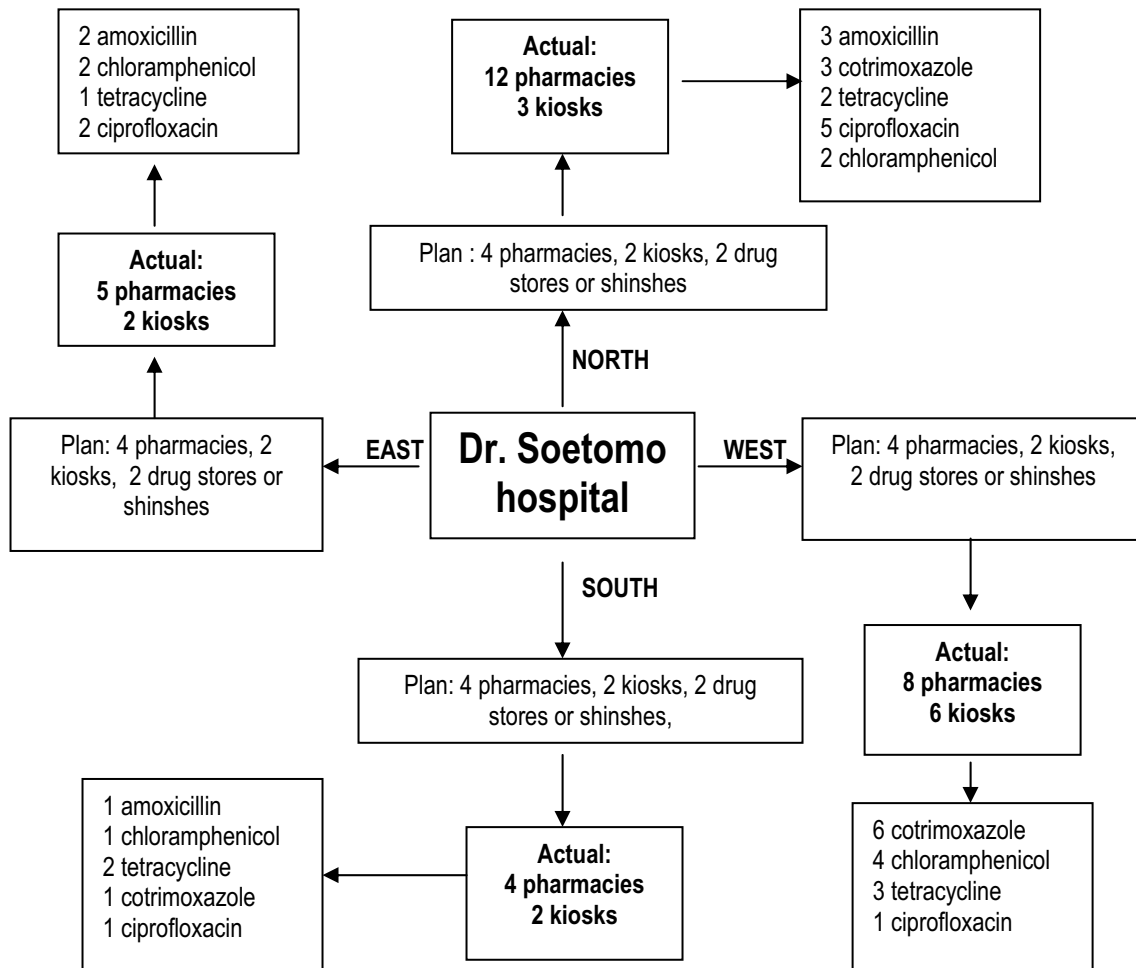


Fig.1b

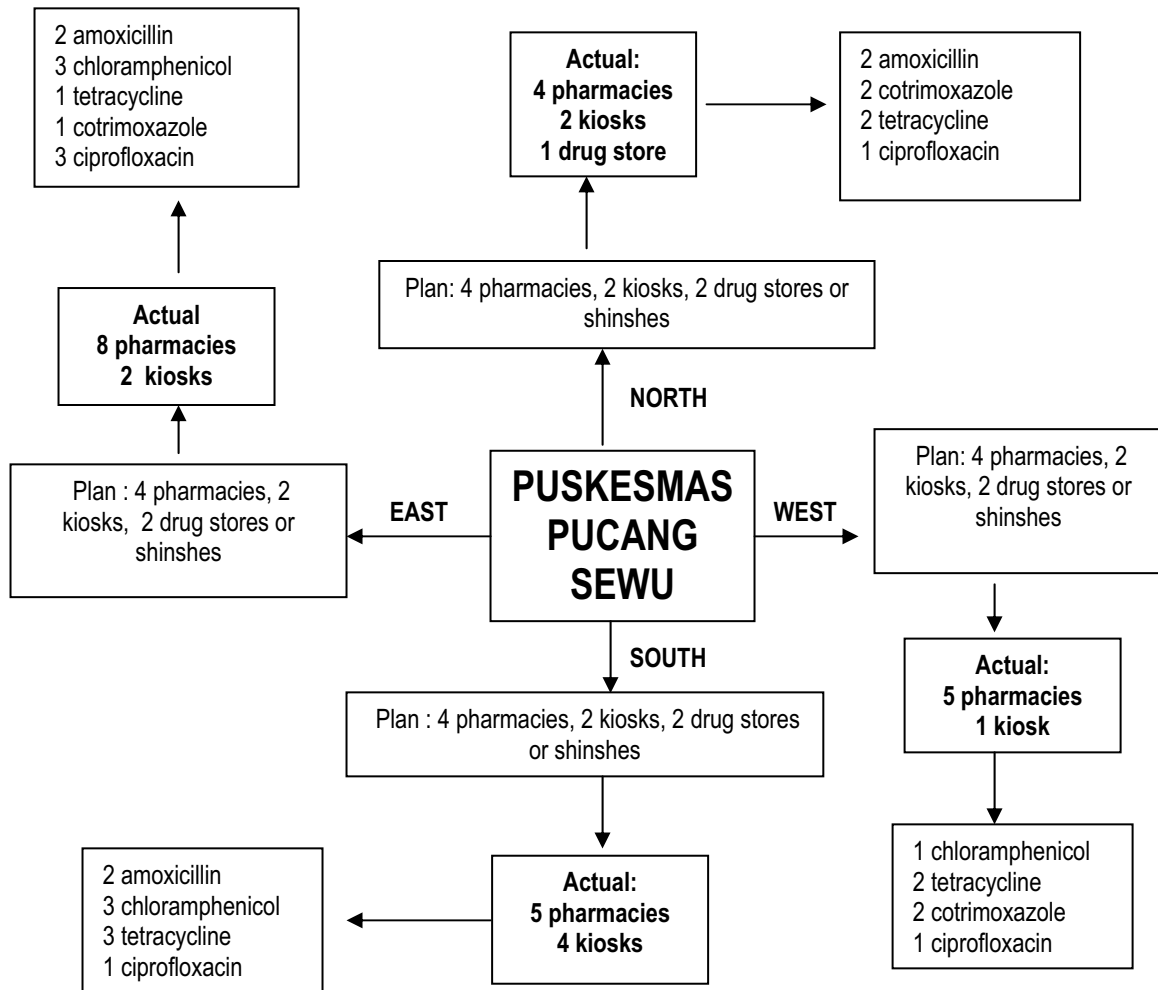
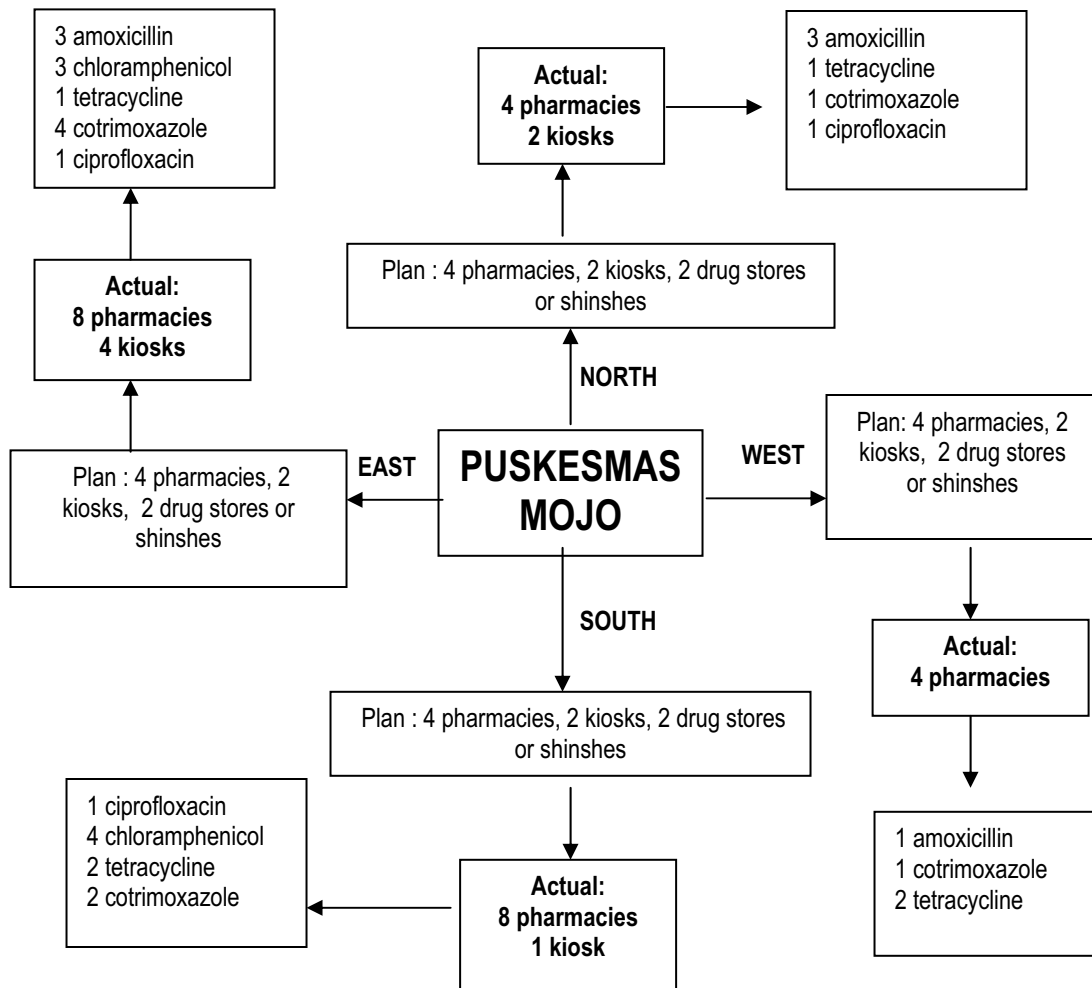


Fig. 1c



Photograph 1



Photograph 2 A.



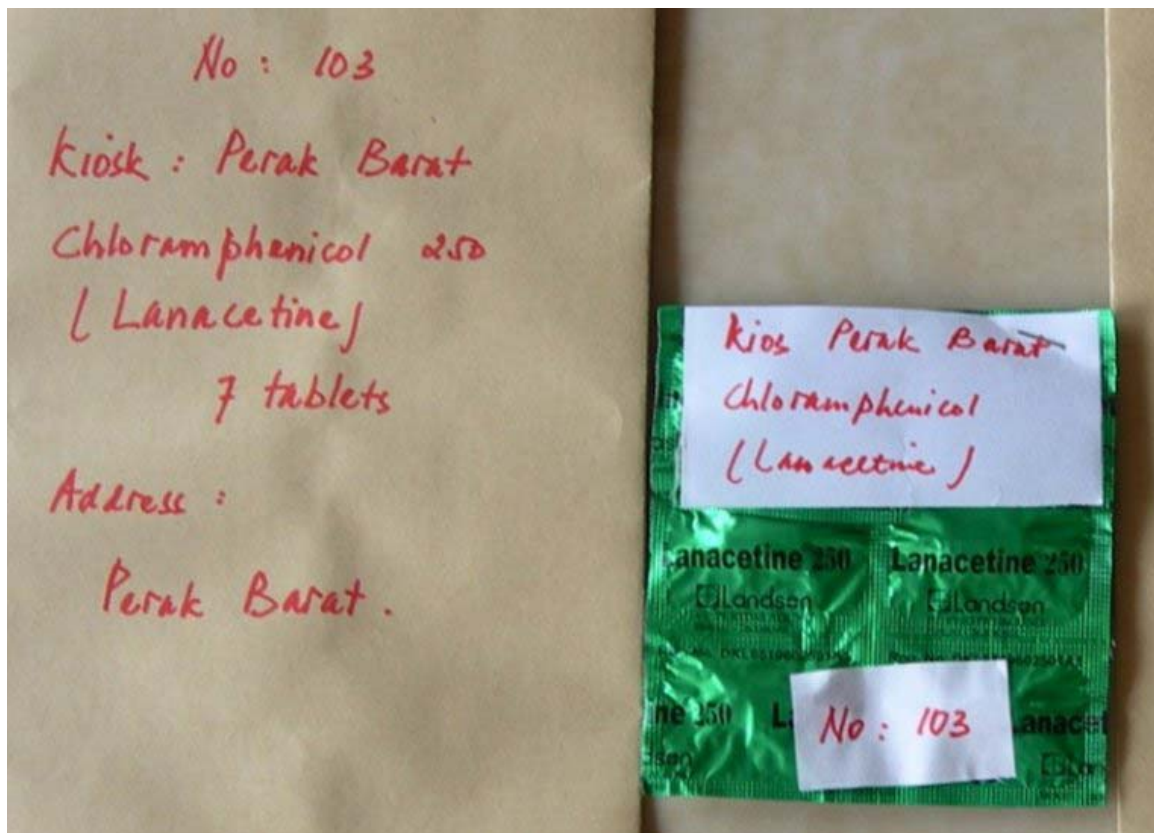
Photograph 2 B.



Photograph 3



Photograph 4 A.



Photograph 4 B.

