Adverse Reactions of 300 MG Diethylcarbamazine, and in a Combination of 400 MG Albendazole, for a Mass Annual Single Dose Treatment, in Migrant Workers in Phang Nga Province

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Background: *Foreign migrant workers with work permits in Thailand are given once a year 300 mg diethylcarbamazine (DEC) for bancroftian filariasis, and 400 mg albendazole (ABZ) for helminthiasis. Treatment effectiveness, tolerability, and safety of two treatment arms, DEC + ABZ and DEC alone, had never been fully documented.*
Objective: *Evaluate the tolerability of the two treatment arms and analyze the effects of adverse reaction, prevalence, and intensity of both common and uncommon adverse drug reactions (ADR) in relation to the reaction time (2 hours = acute, > 2 to 24 hours = subacute, and > 24 to 72 hours = latent).*
Material and Method: *A hospital-based clinical study of on-hour-2 treatment with both treatment arms in 280 Myanmar male migrant volunteers (DEC + ABZ = 150, DEC = 130) was conducted in Phang Nga province, southern Thailand. Of these, ADR evaluation at three reaction times was performed using antigenemic (WbAg+) and non-antigenemic (WbAg-) volunteer groups (DEC + ABZ/WbAg+ = 14, DEC/WbAg+ = 12, DEC + ABZ/WbAg- = 8, and DEC/WbAg- = 16).*
Results: *Both drug groups had similarly overall ADR prevalence [5.2% for DEC + ABZ and 5.1% for DEC ($p > 0.05$)], as well as mean ADR_{acute} scores ($p > 0.05$) on hour 2 post-treatment. The four groups had maximum overall prevalence (10% to 40% for $ADR_{subacute}$). It was more likely to show no relationship between treatment arms and WbAg (neither WbAg+ nor WbAg-) with adverse reaction intensity for ADR_{acute}, $ADR_{subacute}$, or ADR_{latent}. Three major specific ADR were fatigue, dizziness, and headache.*
Conclusion: *Adverse reaction prevalence and intensity were independent for WbAg and treatment arm. The DEC + ABZ have no greater effects on ADR development as the DEC does. The common ADR after treatment are not required for symptomatic treatment. The study confirms DEC + ABZ regime can be safe and not toxic for use in mass treatment of those migrants in Thailand and, its value, in a mass annual single dose treatment, is beneficial for the Global Alliance to Eliminate of Lymphatic Filariasis (GAELF).*

Keywords: *Diethylcarbamazine, Albendazole, Adverse drug reactions, Myanmar migrants*

J Med Assoc Thai 2007; 90 (3): 552-63
Full text. e-Journal: *http://www.medassocthai.org/journal*

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Foreign migrant health conditions are social context issues as they burden the health care system, and are regulated by law in Thailand[1]. Cross-border foreign migrants, subjected to renewal of work permit, need a health examination at a registered hospital setting. Following Guidelines on Foreign Migrant Worker Health Services[1,2], large numbers of the registered migrants are given a mass treatment once every year. This mass treatment is a co-administration drug with 300 mg Diethylcarbamazine (DEC) plus 400 mg Albendazole (ABZ). It has been recommended as the mainstay of large-scale transmission control of lymphatic filariasis and helminthiasis[1-3].

A single-dose combination of the drugs has been recommended for use by some national elimination programs in endemic countries for lymphatic filariasis (*Wuchereria bancrofti*, *Brugia malayi*, or co-endemic with both parasites), but not co-endemic for onchocerciasis[4-9]. Given a mass treatment to endemic populations (both amicrofilaremics and microfilaremics), the drugs in a single-dose combination are safe and not toxic[10-14]. The DEC acts as microfilaricide and can be effectively used in a large-scale transmission control of the imported bancroftian filariasis in Thailand. The disease caused by the nocturnally periodic *W. bancrofti* is common in at-risk Myanmar migrants[15-18]. In addition, the ABZ acts as an anthelminthic drug and can be broad-spectrum effective against helminthiases[5-6,10]. It can be effectively used for treatment of intestinal nematode worms present in those Myanmar migrants[3]. However, due to movement of large numbers of those migrants in Thailand, such intervention available at provincial level and its effects had never been reported. Therefore, treatment effectiveness with a view of tolerability and safety of the drugs needs to be fully documented.

Two groups of Adverse Drug Reactions (ADR) are usually self-limited and characterized by generalized and localized reactions. Adverse reaction intensity with an increased frequency appears as early as 2 hours post-treatment and peaks at 48 hours[11,13,14,19]. Frequency and severity of such side-reactions rely on microfilarial loads in the patient[10,11,14,19]. Adverse reactions are related to the individual's immune inflammatory response to dying parasites[20]. In general, as to the possibility of such side-reactions of DEC, adverse reactions in experienced people have been more often reported. Therefore, such single-dose DEC + ABZ, or DEC alone, raises concerns about either common or uncommon adverse reactions, when applied to a mass treatment to the target population[3]. This will help the authors to confirm tolerability in those co-administered with the safe drugs and hence proper management of ADR, in passive surveillance in the eligible foreign migrant workers.

Phang Nga Provincial Public Health Office (PPHO), Ministry of Public Health (MoPH), has a primary mandate for the management of migrant workers' health conditions and cares. The clinical laboratory diagnosis and treatment of the parasitoses have been the responsibility of the hospitals. Compared with 300 mg DEC, a single-dose treatment with 300 mg DEC + 400 mg ABZ was carried out using the eligible Myanmar population sample who attended to the examination of health conditions in the province. In this hospital-based clinical study, the objectives and study benefits were therefore to evaluate adverse reactions prevalence and intensity.

Material and Method

Study area, population, and consent

The essential clinical trial study with pre-treatment survey of adverse general health outcomes was carried out in Phang Nga province, where the migrant health conditions are one of the major causes of public health problems[1]. Phang Nga, 226 km south of Myanmar-neighboring Ranong province, has seven districts. Similar to that of Ranong[22], all of the districts have the same major Myanmar migrant population in workplace settings. The adult males are predominant in both agriculture and industry. The residence locations as surveyed sites were in Thakua Thung district where they settled down with some job security. To legally renew their work permits, they were all given the MDA with the DEC + ABZ, and the volunteers with $\geq$ 15 years of age were used in both pre- and post-treatment surveys. The oral and/or informed consents with permission of the employers were obtained for all the volunteers.

Pre-treatment survey of adverse general health outcomes

Their adverse general health outcomes or Adverse Effects (AE) occurring in relation to settlement and occupation patterns are common[21]. In the authors' experience, the AE are related to Myanmar population characteristics (*e.g.* age, gender, and previous exposure to DEC). To generalize the AE, a constructed health survey form was used in the present study. It was developed using baseline migrant health status recorded by the health centers in the study area. It comprised of two parts; personal demographics (*e.g.*

age, gender, and DEC treatment history) and 25 questions of the self-reported symptoms (*i.e.* common and uncommon AE that occurred in the past month)[21]. It was translated into Myanmar language by a Myanmar medical doctor at the Faculty of Public Health, Mahidol University. In August 2004, a pre-treatment survey by house-to-house visits was done by a well-trained health survey team, including a Myanmar translator, health personnel as note takers (*e.g.* professional nurse, public health worker and malaria field worker), and a driver. Ninety respondents between the age of 20 and 45 years, including 63 males and 27 females, were used. They were informed about the purposes and significance of the present study in association with the Myanmar translator. The meanings of the questions and severity classification of the symptoms that they experienced in the past month were cleared.

Evaluation of adverse general health outcomes

According to a modification of the method described by Jaturabundit et al[21], frequencies of the 25 symptoms were graded with severity classification (mild, moderate, and severe). The 'Mild' symptom was defined as an episode of the symptom that developed for day(s), once during the past month and treatment was not required for recovery. The 'Moderate' symptom was defined as episodes of the symptom that developed for day(s) and repeated twice during the past month and treatment was not required for recovery. The 'Severe' symptom was defined as episodes of the symptom that developed for at least four consecutive days within a week and repeated twice or more during the past month and treatment was required for recovery. The 'Total Yes' was defined as persons who responded mildly, moderately, or severely. The 'No' was defined as persons who responded not at all. In addition, personal demographics were recorded and then translated into English language by the Myanmar translator.

The Adverse Effect Scores (AES), adjusted to normalize collective data of the 25 graded symptoms, were derived. The AES is a proportion of frequencies of the symptoms graded with 'Total Yes', 'Mild', 'Moderate', or 'Severe', that were divided by frequencies of the symptoms graded with 'No'. All the 25 symptoms with the highest and lowest $AES_{total\ yes}$ values in order, included body ache, fatigue, headache, fever, joint stiffness (stiffness in several joints), myalgia (general muscle aches or pains), stomach cramps, malaise, constipation, dizziness, increased appetite, nausea, double vision, flatulence, vomiting, anorexia (decreased, or loss of, appetite), dry mouth,

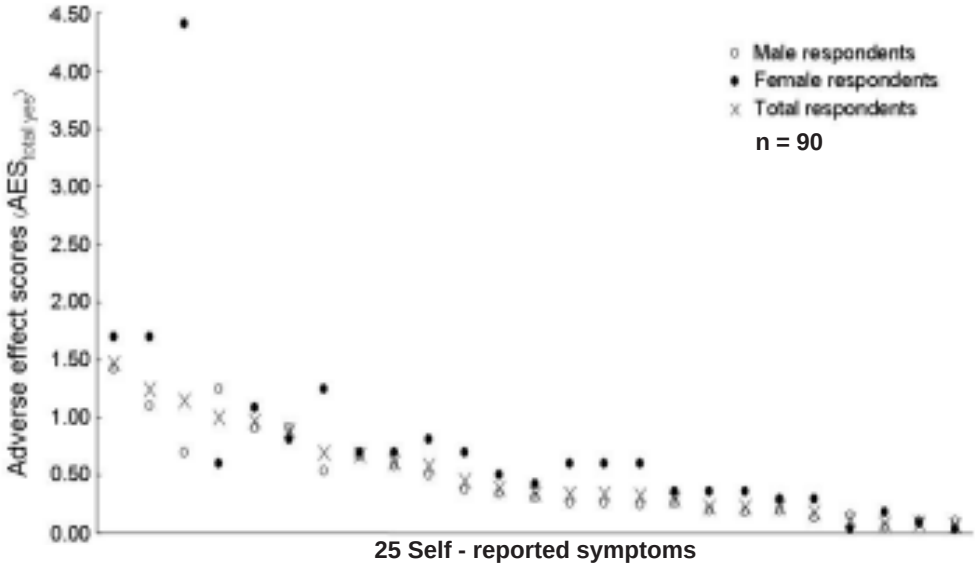

Fig. 1 Adverse effect scores ordered by decreasing the $AES_{total\ yes}$ values for the 25 self-reported symptoms as described in the text, are shown for adverse reaction intensity in the 90 respondents ( ), including 63 males (•) and 37 females (o). In addition, as similar to that for the AES_{mild} and $AES_{moderate}$, mean score for the $AES_{total\ yes}$ is not significantly different between genders. Higher mean score for the AES_{severe} was dependent for the females (Mann-Whitney *U* test, p = 0.027)

rash/skin irritation, persistent cough, joint pain (pains without warmth, swelling, or redness, in several joints), diarrhea, urticaria, wheezing (including bronchial asthma), seizures/convulsion, and swelling of the lymph nodes (Fig. 1). The significant mean scores (*i.e.* $AES_{total\ yes}$, AES_{mild}, $AES_{moderate}$, or AES_{severe}) were analyzed for gender-independent, adverse reaction intensity among the Myanmar subjects. Finally, excluding the swelling of the lymph nodes, the constant $AES_{total\ yes}$ values for the 24 symptoms (a_i; i = 24) (Fig. 1), reported by male respondents, were used as multiplication factors for further calculation of ADR scores in post-treatment surveys.

Subject recruitment, diagnosis, and treatment

The 280 Myanmar male migrant volunteers were selected on admission at the Out Patient Department (OPD) of the Thakua Thung Hospital in September 2004 as cumulative cases. They were physically examined for overt clinical features by the first author. Vital signs, such as body temperature, blood pressure, pulse rate, and respiratory rate, were recorded. Urine and intravenous blood samples were tested for the presence of drug abuse (amphetamines) and contagious syphilis (third-stage infection). The chest X-ray examination was tested for the presence of pulmonary tuberculosis (acute or chronic). No suspected cases were excluded from the present study. In addition, the same blood samples in individuals were examined for a complete blood count, *W. bancrofti* Microfilariae (WbMf) and Antigenemia (WbAg). The *W. bancrofti* antigen detection methods, including Og4C3 Enzyme-Linked Immunosorbent Assay (ELISA) and Immuno Chromatographic Test (ICT), were described elsewhere[17].

After complete examinations, all the cumulative cases were randomly assigned with enumeration list into two drug groups: a single-dose combination of 300 mg DEC + 400 mg ABZ (n = 150); a single-dose 300 mg DEC alone (n = 130). They were orally administered with the drugs, as described elsewhere[3], before the hospital team. Any subjects who developed ADR or even severe adverse event (SAE)[7,8] during or after hospital visit were given symptomatic treatment.

Statistical analysis

Baseline characteristics of two drug groups were presented using descriptive statistics. The Mann-Whitney *U* test, or Student's *t*-test, for two independent samples ($p < 0.05$) was 2-tail, analyzed to compare means or geometric means (GM). Differences in percentages between the groups were analyzed using the χ^2 test. Friedman and Kruskall Wallis tests were used when comparisons were made with more than two groups.

Post-treatment surveys and evaluation of ADR

The evaluation of ADR was blind performed by a different well-trained hospital team. It was based on interviewing and inter-observer judgment, in assistance with the Myanmar translator. The individual's ADR report used in the present study comprised three parts of personal demographics, clinical data, and evaluation of ADR 1-30 (including 24 generalized and six localized ADR). The 24 generalized ADR as previously described were used. The six localized ADR included funiculitis, epididymitis, lymphadenitis, adenolymphangitis, lymphangitis, and orchalgis. Based on pharmacokinetics of the drugs and pharmacovigilance in treated people[11-14,19], the reaction time classification and grading of ADR were used in the present study as follows: No = 1, Acute = 2, Subacute = 3, Latent = 4. The 'Acute' reactions were defined as adverse reactions that developed within 2 hours post-treatment. The 'Subacute' reactions were defined as adverse reactions that developed > 2 hours to 24 hours post-treatment. The 'Latent' reactions were defined as adverse reactions that developed > 24 hours to 72 hours or longer after treatment. The 'No' defined as male subjects who had no ADR. The calculation of ADR scores was performed using following formulas I toV:

$$\frac{[P]}{[Q]} \times 100 \quad \ldots\ldots\ldots\ldots \text{I}$$

$$P' = Q - P \quad \ldots\ldots\ldots\ldots \text{II}$$

$$\frac{[2(a_i) \times P]}{[1(a_i) \times P']} \quad \ldots\ldots\ldots\ldots \text{III}$$

$$\frac{[3(a_i) \times P]}{[1(a_i) \times P']} \quad \ldots\ldots\ldots\ldots \text{IV}$$

$$\frac{[4(a_i) \times P]}{[1(a_i) \times P']} \quad \ldots\ldots\ldots\ldots \text{V}$$

For instance, 'Acute' symptom frequency (%) is expressed by formula I, where P is the number of subjects that developed the 'Acute' symptom, and Q is the total of subjects in the group. Formula II, the P' is the number of subjects that did not develop the 'Acute' symptom on hour 2 post-treatment. Then, ADR_{acute} score of the symptom (a_i; i = 30) is automatically calculated using formula III. In a similar manner, 'Subacute' or

'Latent' symptom frequency is expressed by formulas I and II. In addition, ADR intensity scores for $ADR_{subacute}$ or ADR_{latent} are calculated using formulas IV and V, respectively. In other words, overall prevalence of ADR (%) is mathematically expressed as:

$$\frac{\left[\sum_{i=1}^{n} P_i\right]}{[aQ]} \times 100$$

Where a_i is combined ADR (24 for generalized ADR or six for localized ADR)

$\sum_{i=1}^{n} P_i$ is a total number of subjects with combined ADR

To evaluate adverse reaction prevalence and intensity between the drug groups that responded to reaction time as early as 2 hours post-treatment[12], frequencies of any symptoms (ADR 1-30) developed on hour 2 were recorded and graded, regardless of the *W. bancrofti* antigenemia among the 280 Myanmar subjects. The ADR_{acute} frequency and intensity was performed. The Mann-Whitney *U* test was used to describe significant mean scores. The χ^2 test was used to describe significant differences in prevalence (%) of generalized or localized ADR between the drug groups, as mentioned above.

However, in the presence of the active *W. bancrofti* infection, frequencies of any symptoms (ADR 1-24) developed on hours 2, 24 and 72 post-treatment were recorded and graded. According to this, the antigenemic (ICT-positive) and ICT-negative volunteers as negative control were matched with age and treatment arm. All the four groups: A, DEC + ABZ/WbAg+ (n = 14); B, DEC/WbAg+ (n = 12); C, DEC + ABZ/WbAg- (n = 8); D, DEC/WbAg- (n = 16), were used. Effects of the treatment arms versus WbAg+, as well as WbAg-, on adverse reaction intensity (*i.e.* mean score for ADR_{acute}, $ADR_{subacute}$, or ADR_{latent}) in all the four groups were tested using Mann-Whitney *U* test. The Friedman test, or Kruskall Wallis test, was used to describe significant differences in mean scores. Significance was set at $p < 0.05$.

Results

W. bancrofti antigenemic infection prevalence and intensity

Of the 280 subjects aged 17 to 56 years (mean $\pm$ SD = 29.9 $\pm$ 7.3) that were parasitologically and serologically examined, none was microfilaremic. The overall antigenemia rate was 18.9% (Table 1). Group I (DEC + ABZ) had antigenemia prevalence (24.8% WbAg rate) and intensity (GM WbAg load = 14,566 AU/ml). Group II (DEC) had 17.7% of WbAg rate and higher intensity (GM WbAg load = 32,407 AU/ml). However, there were no significant differences in WbAg infection prevalence and intensity between the drug groups ($p > 0.05$).

Table 1. Baseline characteristics of the subjects[a] between the drug groups

Characteristic	DEC $\pm$ ABZ (n = 150)	DEC (n = 130)	p-value[b]
Age (years)	28.5$\pm$7.3	31.5$\pm$7.0	<0.001
Hematological findings:	(n = 125)	(n = 124)	
White blood cell (4.6-10.2 K/μl)	8.3$\pm$1.8	7.1$\pm$2.7	<0.001
Lymphocyte (10.0-50.0 %)	34.2$\pm$7.5	46.5$\pm$13.8	<0.001
Neutrophil (37.0-80.0 %)	48.2$\pm$8.8	34.6$\pm$15.8	<0.001
Monocyte (0.0-12.0 %)	6.0$\pm$1.6	6.7$\pm$2.6	0.008
Eosinophil (0.0-7.0 %)	9.9$\pm$5.5	8.3$\pm$5.4	0.01
Basophil (0.0-2.5 %)	1.6$\pm$0.7	3.1$\pm$2.2	<0.001
Blood pressure (mm Hg):			
Systolic	123.8$\pm$12.5	120.4$\pm$11.8	0.013
Diastolic	75.6$\pm$9.2	75.2$\pm$8.6	0.806
Body temperature (C)	37.0$\pm$0.3	37.0$\pm$0.4	0.354
Respiratory rate (times/min)	20.9$\pm$1.2	20.3$\pm$0.9	<0.001
Pulse rate (times/min)	80.6$\pm$9.0	76.0$\pm$9.6	<0.001
WbAg infection prevalence (%)	31/125 (24.8)	22/124 (17.7)	0.228[c]
WbAg load (AU/ml)	14,566.0	32,406.9	0.255[c]

Abbreviation: AU/ml = antigen units per milliliter, K/μl = 10^3 cells/μl, WbAg = *W. bancrofti* antigenemia
The data are presented as mean $\pm$ SD and GM (AU/ml). For hematology, normal range is presented in parentheses
[a] None was microfilaremic. [b] Mann-Whitney *U* test, or χ^2 test[c], for two independent samples, were used

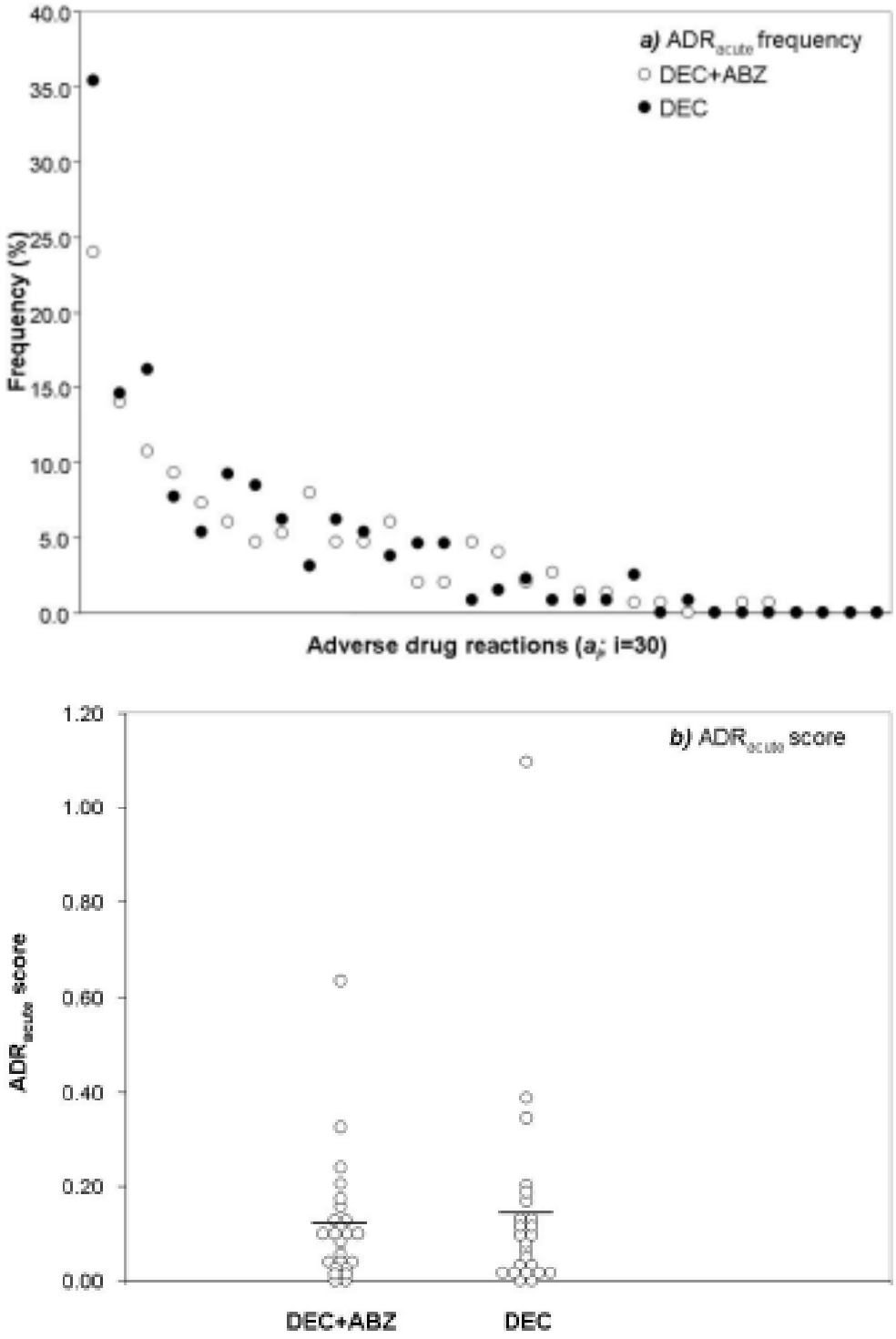

Fig. 2 Adverse drug reactions (ADR) developed on hour 2 post-treatment in the 280 Myanmar subjects. Both generalized and localized ADR (a_i; i = 30), ordered by decreasing frequency as described in the text, between the drug groups: DEC + ABZ (o) and DEC (•) are shown in Fig. 2a. The adverse reaction intensity (*ie* mean ADR_{acute} score denoted as the bars) of the 24 generalized ADR between the groups is shown in Fig. 2b. The calculation of ADR_{acute} score for the 6 localized ADR was not applicable

In addition, of the 31 WbAg+ subjects of group I (Table 1), there were 14 WbAg+ subjects evaluated for ADR (or group A) (GM = 23,432 AU/ml) while there were 17 WbAg+ subjects with loss to follow-up (GM = 9,847 AU/ml) (data not shown). Group II included 12 WbAg+ subjects (or group B) (GM = 56,021 AU/ml) and 10 WbAg+ subjects with loss to follow-up (GM = 16,803 AU/ml) (data not shown). There was no significant difference in mean WbAg loads between A and B groups (t = -1.790, p = 0.086) (data not shown).

Adverse reaction prevalence and intensity on hour 2

When comparing the ADR_{acute} frequencies between the drug groups, the ADR 1-30, ordered by decreasing frequencies, included dizziness, headache, nausea, increased appetite, fatigue, malaise, stomach cramps, body ache, dry mouth, decreased appetite, myalgia, persistent cough, fever, flatulence, double vision, joint pain, constipation, joint stiffness, vomiting, diarrhea, wheezing, rash/skin irritation, urticaria, seizures/convulsion, funiculitis, epididymitis, lymphadenitis, adenolymphangitis, lymphangitis, and orchalgis, respectively (Fig. 2a). The first 8 ADR had frequencies greater than 5%. Of these, uncommon ADR were increased appetite and stomach cramps. Group I had localized ADR (an overall prevalence of 0.2%): the same 0.7% of funiculitis and epididymitis was found. Group II did not develop any localized ADR. The overall prevalence of the combined 24 generalized ADR was 5.2% (for group I) and 5.1% (for group II) (data not shown). There was no significant difference in overall prevalence (for ADR_{acute} frequency) between the groups (p > 0.05). In addition, when analyzing ADR_{acute} frequency in each of the 24 generalized ADR, both groups had the likelihood of common adverse reactions (p > 0.05 or p = 0.05) (data not shown). In other words, adverse reaction intensity was universal for both groups: mean ADR_{acute} scores were not significantly different (Z = -0.124, p = 0.901) (Fig. 2b).

Adverse reaction prevalence and intensity in relation to W. bancrofti infection

When ADR development in the presence or absence of *W. bancrofti* antigenemia was analyzed, all the four groups (A to D) were evaluated for adverse reaction prevalence and intensity on hours 2, 24 and 72 post-treatment. The overall prevalences were analyzed using the combined eight major specific ADR (headache, dizziness, fatigue, body ache, nausea, myalgia, malaise, and fever). Two common ADR (myalgia and fever) were considered instead of the uncommon ADR. It was more likely to show high prevalence (for

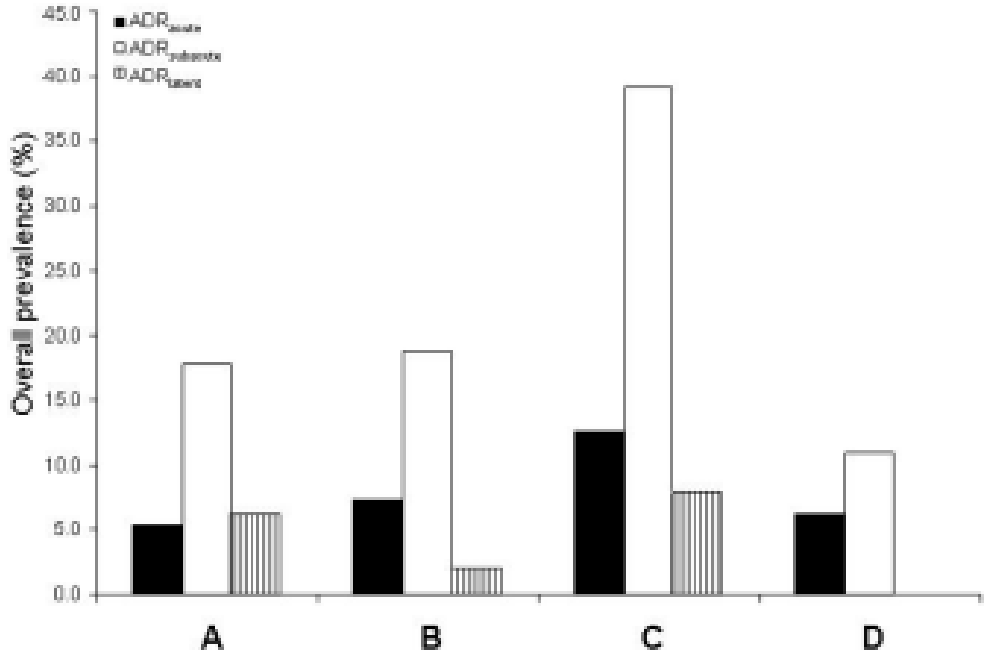

Fig. 3 Overall prevalences (% of ADR_{acute}, $ADR_{subacute}$, or ADR_{latent} frequency), using the combined 8 major specific ADR, in the four groups: A, DEC + ABZ/WbAg+ (n = 14); B, DEC/WbAg+ (n = 12); C, DEC + ABZ/WbAg- (n = 8); D, DEC/WbAg- (n = 16)

Table 2. Effects of the treatment arms on adverse reaction intensity

Group		Mean ± SE		
		ADR_{acute}	$ADR_{subacute}$	ADR_{latent}
WbAg+	A	0.099±0.043	0.526±0.120	0.432±0.141
	B	0.193±0.120	0.952±0.481	0.091±0.06
WbAg-	C	0.402±0.243	1.082±0.601	0.0
	D	0.143±0.057	0.764±0.205	0.172 ± 0.074

W. bancrofti infection status: WbAg+ = antigenemia, WbAg- = non-antigenemia

The data which were derived using collective ADR scores for the 8 major specific ADR in each (n) of the 4 groups A to D (14, 12, 8, and 16, respectively) and, in groups B and C, asymptotic significance with Shapiro-Wilk test ($p < 0.01$) is shown Significant ($p < 0.05$) with Friedman test, Kruskall Wallis test for four independent samples, and Mann-Whitney *U* test for two independent samples

$ADR_{subacute}$ frequency) of common adverse reactions that peaked at > 2 hours to 24 hours post treatment in all the four groups: degrees of overall prevalence (10% to 40%) are shown (Fig. 3). Lower prevalence varied from 5% to 12% for ADR_{acute} frequency, and up to 8% for ADR_{latent} frequency.

When effects of treatment arms versus WbAg (or WbAg+) between groups A and B were analyzed, there were no significant differences in mean scores for ADR_{acute}, $ADR_{subacute}$, or ADR_{latent} (Mann-Whitney *U* test, $p > 0.05$) (Table 2). Similar to groups C and D in the absence of the WbAg (or WbAg-), there were no significant differences in mean scores for ADR_{acute}, or $ADR_{subacute}$. However, significance was noted for ADR_{latent} ($Z = -2.219$, $p = 0.027$). When mean scores for ADR intensity (ADR_{acute}, $ADR_{subacute}$, and ADR_{latent}) were analyzed, significant mean scores for groups C and D were noted (Friedman test: $\chi^2 = 6.381$, df =2, $p = 0.041$; $\chi^2 = 6.276$, df =2, $p = 0.043$, respectively) (Table 2). Significant differences in mean scores for ADR_{latent} for all the four groups were also noted (Kruskall Wallis test, $p = 0.027$).

Discussion

Reports of the ADR in the population are essential for health personnel to reflect proper management in pharmaceutical cares and ethics in public health[8,9,13,23]. In particular, a vast majority of those migrants renewing work permits in Thailand has been targeted for a mass annual single dose treatment with DEC and albendazole once every year[1,2,24]. Such drugs in a single-dose combination recommended for large-scale controlling the parasitoses commonly observed among them need to be evaluated and monitored timely as to whether treatment effectiveness is achievable on a wide scale. However, such findings compared well with previous findings[21] that the AE in terms of the AES elicit a baseline for their health conditions susceptible for responses to various exposures (*e.g.* agents, chemicals, particles, and drugs) in the study area. Therefore, the tolerability and safety of the drugs reported by the individual recipients in the present study were discussed, on both common and uncommon adverse reactions after treatment. This would be critical for providing proper management to many of those migrants with high background of adverse general health outcomes. Adaptive or acquired health outcomes in relation to their settlement and occupation patterns may be a vulnerable factor that favors risks for compliance and coverage of the MDA program. Improper management and insufficient supervision of health personnel would otherwise have arisen to concern about negative effects to the MDA program. These may lead to rejection of treatment, treatment delay, and avoidance of seeking health care[22].

Previous studies demonstrated that adverse reactions of the drugs are independent of ages and genders[11,13,14]. In general, after treatment with either DEC alone or DEC+ABZ regimen, any developed adverse reactions would likely be systemic reactions that directly respond to the treatment arms. This implies Myanmar male migrants could respond to the treatment arms with a view of dose-dependent tolerability in the present study. In addition, adverse reactions peak at a few hours or on day(s) post-treatment. However, because of no systemic reviews, such incidence or prevalence of major adverse reactions would serve as a baseline for passive surveillance or point-of-care monitoring of ADR in those receiving the drug regimens in the area. This was a reason why the structure

of the ADR report in individuals had been developed, using AE baseline, before the present study.

In post-treatment survey using the ADR 1-24 (Fig. 2), common adverse reactions showed high prevalence (% ADR_{acute} frequency), 35% to > 10% for dizziness, headache, and nausea, respectively. However, slightly lower prevalence was 10% to 2% for fatigue, malaise, body ache, myalgia, and fever, respectively. This agreed with the previous findings[19] that three major specific generalized ADR (dizziness, myalgia, and headache) in *Brugia malayi* microfilaremic (BmMf) patients in Indonesia were recorded 2 hours after 6 mg/kg DEC intake. Major generalized ADR in endemic normals (dizziness and myalgia) and in elephantiasis patients (dizziness and headache) were more compliant. Dizziness was transient 24 hours to 32 hours post treatment in two latter groups. In the present study, the adverse reaction prevalence for uncommon ADR was 9% to 2% for increased appetite, stomach cramps, dry mouth, anorexia, persistent cough, and flatulence, respectively. When evaluated for the 6 localized ADR on hour 2 post-treatment, DEC + ABZ group had one 26-year-old subject (WbAg-) with localized ADR (funiculitis and epididymitis), with no abnormal limits of hematological findings (except for eosinophil count of 13.7%) and vital signs. Two drug groups tolerated well and none had SAE, or required symptomatic treatment. Even three subjects with vomiting (1%) in both drug groups in the present study were reported, but all had required no symptomatic treatment. In addition, according to baseline information about migrant health conditions in the area, the gastrointestinal conditions (stomach cramps, flatulence, diarrhea, and constipation) were common among them. These ADR may be adaptive or acquired and were expected to occur once after treatment. They were all not considered as specific ADR. However, when the combined ADR 1-24 were used, both drug groups had the same overall prevalence (of 5%) and intensity as shown in Fig. 2. Perhaps, both drug regimens concentration on hour 2 reaction time[12] did not have significance in subside reactions development or require symptomatic treatment in the groups. Taken together, high degrees of adverse reaction prevalence were the likelihood of baseline health outcomes after receiving the treatment arms. However, the eight major specific ADR (headache, dizziness, fatigue, body ache, nausea, myalgia, malaise, and fever) could be observable and measurable health outcomes in the Myanmar subjects.

In India, Pani et al[11] reported WbMf patients had high incidences of generalized ADR (fever, headache, and myalgia) in three drug groups (DEC + ABZ > DEC > ABZ). Similar to the data published by El Setouhy *et al*[12], these major specific ADR peaked on day 2 post-treatment in all drug groups, and were transient on day 6 post-treatment. In some BmMf cases, adverse reactions (dizziness, headache, and myalgia) were not transient (beyond 120 hours post-treatment)[19]. Albendazole alone had a mean score significantly lower than either DEC alone or DEC + ABZ. Two latter groups had similar adverse reaction intensity.

In the present study, when using the combined eight major specific ADR, adverse reaction prevalence in the four groups was evaluated for peak reaction time. Regardless of the *W. bancrofti* antigenemia (WbAg), all the four groups tolerated well and had maximum overall prevalence (10% to 40% of $ADR_{subacute}$ frequencies), or had high mean scores for $ADR_{subacute}$ intensity. Three major specific ADR (fatigue, dizziness, and headache) were frequently reported. Fatigue was more frequently compliant (22 of the 50 subjects reported), or peaked at subacute reaction time (> 2 hours to 24 hours). Fewer numbers (the same 12 of the 50 reported) had dizziness and headache. It was more likely to show dizziness was transient between > 24 hours and 72 hours (latent reaction time), but fatigue was transient on either acute or latent reaction time. On the other hand, when effects of treatment arms versus WbAg were analyzed, effects of the treatment arms on adverse reaction intensity, as similar to prevalence, were shown for both WbAg+ and WbAg- groups. Such findings come with the fact that the treatment arms' effects on adverse reaction intensity (ADR_{acute}, $ADR_{subacute}$, or ADR_{latent} scores) were not associated with the WbAg. That is, ABZ had no added-in effects on adverse reaction prevalence and intensity, and hence DEC+ABZ had no greater effects as the DEC did. Contrary to WbAg, adverse reactions are positively correlated with Mf density[10,11,14,19]. Although none had microfilaremia, it is believed that this phenomenon may occur in Myanmar microfilaremics and need for further ADR evaluation. Therefore, adverse reaction prevalence and intensity after treatment with both treatment arms peaked at the same subacute reaction time, > 2 hours to 24 hours post-treatment, in the Myanmar population tested. Such adverse reactions were independent for WbAg and treatment arm.

In conclusion, Myanmar migrant workers receiving a mass annual single dose treatment with DEC + ABZ or DEC alone tolerated it well. Three major specific adverse reactions (fatigue, dizziness, and

headache) were more compliant, > 2 hours to 24 hours post treatment. Such proper management of common ADR at their site would emphasize on the basis of personal-focused hygiene and self-efficacy health care. The present study confirms DEC + ABZ regimen, as similar to DEC alone, can be safe and not toxic for use in mass treatment of those migrants with work permits in Thailand. In particular, its value in a mass annual single dose treatment is beneficial for the Global Alliance to Eliminate of Lymphatic Filariasis (GAELF)[7,8,23].

Acknowledgements

The study was supported by a grant from the PPHO, MoPH, Phang Nga. The authors are grateful to Dr. Jesuda Chaikunrat, Phang Nga Provincial Chief Medical Officer, PPHO, and to Takua Thung Hospital's staff, for their technical support. We wish to thank professional nurses, Ms. Suree Kanprakob, Mrs. Puttana Kittikanjanapa, Mrs. Prapa Sirikul, Ms. Alauma Thongmee, Mrs. Wanna Wunbua, Mrs. Sutussa Lanthong, Ms. Vipavee Puchadapirom, Ms. Madta Phrompud, and Ms. Daungkamol Kolrean, and the Myanmar translators for their help in data collection. We wish to thank Dr. Ko Ko Maung, Faculty of Public Health, Mahidol University, for critical review of health survey form and translation into Myanmar language. We wish to thank Mr. Anucha Sampuch, Thap Put Hospital, and Mr. Piya Yamboonreung, Takua Pa Hospital, MoPH, Phang Nga, for clinical laboratory diagnosis of the infectious conditions of the Myanmar participants recruited into the study.

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อาการไม่พึงประสงค์หลังจากกินยาของการรักษาแบบรับประทานปีละครั้งด้วยยาไดเอทธิลคาร์บามาซีน ขนาด 300 มิลลิกรัม และร่วมกับยาอัลเบนดาโซลขนาด 400 มิลลิกรัม ในแรงงานอพยพในจังหวัดพังงา ประเทศไทย

พิสิฐ ยงยุทธ, สุรชาติ โกยดุลย์, นงนุช จตุราบัณฑิต, วุฒิศาล จริยหัตถะกิจ, อดิศักดิ์ ภูมิรัตน์

***ภูมิหลัง**: แรงงานต่างด้าวอพยพที่มีใบอนุญาตประกอบอาชีพในประเทศไทย ได้รับการรักษาด้วยยาไดเอทธิลคาร์บามาซีน (DEC) ขนาด 300 มิลลิกรัม (มก.) สำหรับโรคฟีลาเรียชนิดแบนครอฟไต และยาอัลเบนดาโซล (ABZ) ขนาด 400 มก. สำหรับโรคหนอนพยาธิ ประสิทธิผลของการรักษาในด้านความสามารถในการต้านความเป็นพิษและความปลอดภัยของยาทั้งสองขนาน (DEC+ABZ และ DEC เพียงชนิดเดียว) ยังไม่เคยได้รับการศึกษาอย่างถ่องแท้ในกลุ่มเหล่านี้*

***วัตถุประสงค์**: ประเมินความสามารถในการต้านความเป็นพิษของยาทั้งสองขนาน เพื่อวิเคราะห์ผลกระทบของการออกฤทธิ์ของยาต่อความชุกและความรุนแรงของการเกิดอาการไม่พึงประสงค์หลังจากการกินยา (ADR) ทั้งที่เกิดขึ้นบ่อยและไม่เกิดขึ้นบ่อย ตามระยะเวลาการออกฤทธิ์ของยา (2 ชั่วโมง หรือ acute, มากกว่า 2 ถึง 24 ชั่วโมง หรือ sub-acute, มากกว่า 24 ถึง 72 ชั่วโมง หรือ latent)*

***วัสดุและวิธีการ**: การศึกษาทางคลินิกของการรักษา 2 ชั่วโมงหลังจากการกินยาด้วยยาทั้งสองขนาน ใช้อาสาสมัครแรงงานชาวพม่าเพศชาย จำนวน 280 ราย (DEC + ABZ = 150 ราย และ DEC = 130 ราย) ในจังหวัดพังงา ภาคใต้ของประเทศไทย ในจำนวนกลุ่มอาสาสมัครเหล่านี้ การประเมินอาการ ADR ตามระยะเวลาการออกฤทธิ์ของยาทั้งสามช่วงเวลาใช้อาสาสมัครที่มีฟีลาเรียแอนติเจนในเลือด (WbAg+) และไม่มีฟีลาเรียแอนติเจน (WbAg-) จำนวน 4 กลุ่ม (DEC + ABZ/WbAg+ = 14, DEC/WbAg+ = 12, DEC + ABZ/WbAg- = 8, and DEC/WbAg- = 16)*

***ผลการศึกษา**: 2 ชั่วโมงหลังจากการกินยา ทั้งสองกลุ่มการรักษา มีความชุกของอาการ ADR แตกต่างอย่างไม่มีนัยสำคัญทางสถิติ ($p > 0.05$) คือ 5.2% สำหรับกลุ่ม DEC + ABZ และ 5.1% สำหรับกลุ่ม DEC และเช่นเดียวกับคะแนนเฉลี่ย ADR_{acute} ($p > 0.05$) กลุ่มอาสาสมัครทั้ง 4 กลุ่ม มีความชุกของอาการ ADR ในระดับสูงสุด (10% ถึง 40% สำหรับ $ADR_{subacute}$) และมีแนวโน้มว่า ผลของการให้ยาทั้งสองขนานต่อความรุนแรงของอาการ ADR (ADR_{acute}, $ADR_{subacute}$ หรือ ADR_{latent}) ไม่สัมพันธ์กับฟีลาเรียแอนติเจน อาการ ADR ที่เกิดขึ้นบ่อย ได้แก่ อาการอ่อนเพลีย วิงเวียนศีรษะและปวดหัว*

***สรุป**: ความชุกและความรุนแรงของอาการ ADR ไม่ขึ้นอยู่กับฟีลาเรียแอนติเจนและขนานของยา ยาขนาน DEC + ABZ ไม่มีผลต่อการเกิดอาการ ADR สูงเกินกว่าการใช้ยาขนาน DEC เพียงชนิดเดียว อาการที่เกิดขึ้นเหล่านั้น ไม่จำเป็นต้องได้รับการรักษาตามอาการ ซึ่งการศึกษานี้ยืนยันว่ายาขนาน DEC + ABZ มีความปลอดภัยและไม่มีพิษในการรักษากลุ่มแรงงานต่างด้าวอพยพในหลายพื้นที่ในประเทศไทย และโดยเฉพาะอย่างยิ่งการรักษากลุ่มแบบรับประทานปีละครั้ง เป็นประโยชน์ต่อโครงการความร่วมมือการกำจัดโรคเท้าช้างทั่วโลก (GAELF)*