Risk factors for Lymphatic Filariasis and Mass Drug Administration non-Participation in Mandalay Region, Myanmar

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Research Article

Keywords: Lymphatic filariasis, risk factors, Myanmar, Asia, infection, hydrocoele, mass drug administration, coverage, compliance, participation

Posted Date: August 18th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-59699/v1

Version of Record: A version of this preprint was published on January 22nd, 2021. See the published version at https://doi.org/10.1186/s13071-021-04583-y.

Abstract

Background: Myanmar commenced a lymphatic filariasis (LF) elimination program in 2000. Whilst the country has made considerable progress since then, a number of districts have demonstrated persistent transmission after many rounds of mass drug administration (MDA). The causes of unsuccessful MDA have been examined elsewhere, however, there remains little information on the factors that contribute in Myanmar.

Methods: We conducted an analysis of factors associated with persistent infection, LF-related hydrocoele and MDA participation in an area with ongoing transmission in 2015. A cross-sectional household survey was undertaken in 24 villages across four townships of Mandalay Region. Participants were screened for circulating filarial antigen (CFA) using immunochromatographic tests and if positive, for microfilaria by night-time thick blood slide. Individuals 15 year and older were assessed for filariasis morbidity (lymphoedema and if male, hydrocoele) by ultrasound-assisted clinical examination. A pre-coded questionnaire was used to assess risk factors for LF and for never-taking MDA. Significant variables identified in univariate analyses were included in separate step-wise multivariate logistic regressions for each outcome.

Results: After adjustment for covariates and survey design, being CFA positive was significantly associated with age (odds ratio (OR) 1.03, 95% CI 1.01 – 1.06), per year), male gender (OR 3.11, 1.23 – 7.87), elevation (OR 0.97, 0.94 – 1.00, per metre) and the density of people per household room (OR 1.56, 1.26 – 1.93). LF-related hydrocoele was associated with age (OR 1.06, 1.02 – 1.09, per year) and residing in Amarapura Township (OR 8.56, 1.33 – 55.22). Never-taking MDA was associated with age (less than 15 years: OR 2.89, 1.11 – 7.51; greater than 60 years: OR 4.00, 1.53 – 10.48), male gender (OR 1.85, 1.05 – 3.25), residing in Amarapura township (OR 2.99, 1.39 – 6.43), moving to one's current village from another (OR 2.84, 1.15 – 7.02) and ever having declined medication (OR 13.76, 4.79 – 39.58). Decreased likelihood of never taking MDA was associated with a higher proportion of household members being present during the last MDA round (OR 0.18, 0.04 – 0.96)).

Conclusions: These results contribute to the understanding of LF and MDA participation related risk factors, and will assist Myanmar improve its elimination and morbidity management programs.

Background

Lymphatic filariasis (LF) remains a major cause of permanent disability in tropical and sub-tropical countries.[1] Chronic infection with filarial worms causes lymphatic dysfunction leading to the progressive and irreversible swelling of the limbs and genitals. This results in substantial disability, discomfort, social-stigma and economic disadvantage.

In response, the World Health Organization (WHO) established the Global Program to Eliminate LF in 2000, which is based on two intervention pillars. The first is to interrupt the transmission of LF through mass drug administration (MDA) of an annual dose of anti-filarial medications to at-risk populations.[1]

The medications include albendazole plus either diethylcarbamazine (DEC) or ivermectin, and are administered for a minimum of five consecutive years. The second component is to alleviate the suffering of those with existing LF-related disease through targeted management programs.

Worldwide, the WHO South-East Asian Region has the highest burden of LF.[1, 2] Myanmar (formerly Burma) is one of the most affected countries in this region, with 41 million people (80 percent of the population) at-risk.[3, 4] Filariasis in the country is distributed predominantly in the central and western dry zones, where base-line (pre-MDA) prevalence was 20 to 30 percent.[3–6] The parasite *Wuchereria bancrofti* is the sole reported cause of LF in the country where it is transmitted by the mosquito *Culex quinquefasciatus*.[4, 7]

Myanmar commenced an MDA program with DEC and albendazole in 2001. Since then, the country has made considerable progress toward the elimination of LF, but has also faced a number of challenges.[3–5] Medication supply and financial issues, as well as concerns over the reported incidence of serious adverse reactions, led to the interruption of a number of MDA rounds at both the national and regional level.[3, 8] Whilst treatment coverage across the country has reportedly been high (60.0–100%), actual participation may have been much lower in some areas.[3, 5, 9, 10]

Mass drug administration rounds have led to considerable reductions in LF prevalence in many areas of Myanmar.[3–5] A number of districts, however, have demonstrated persistent transmission despite many rounds of MDA, suggesting that the program there had not been fully successful.[3–5, 9, 10] A number of reasons have been shown to account for the failure of MDA rounds to interrupt transmission in other countries.[11, 12] These include programmatic factors (the delivery and distribution of medication to eligible participants) or those relating to individual compliance (eligible participants taking the offered medication). Whilst there are common trends, the combination of factors that undermines success varies from region to region. Determining the causes of persistent transmission specific to Myanmar is crucial to ensuring effective elimination efforts.

Recently, an independent survey was conducted in four townships of Mandalay region that had demonstrated ongoing transmission.[9] It found that 20 percent of the population had not participated in any of the six rounds of MDA. Of those who had, medication had only been taken on average 2.73 times. While this study provided an accurate estimate of LF burden and MDA participation, there remains no data on the potential causes of ongoing transmission or low medication uptake in Myanmar. We therefore conducted an analysis to determine the factors associated with persistent infection and MDA non-participation in the country. We define ‘non-participation’ in MDA in this context as ‘never taken MDA.’ Never taking MDA could be due to a number of factors, including lack of access (the programme did not reach the person to offer it); absence during MDA; ineligibility due to age < 2 years, severe chronic illness or pregnancy; or active refusal.

Methods

Study setting

Myanmar is a lower-middle income country in Southeast Asia which had a population of 51 million at the 2014 census.[13] The country is administratively divided into a union territory (Naypyitaw), seven states and seven regions. These fifteen administrative areas are further divided into districts, townships, cities, towns, wards, village tracts and villages.

Mandalay Region is situated in the low-lying and dry central plains of Myanmar. The majority of its population (6 million in 2014) live rurally in villages, where the predominant occupation is farming.[13] The region's capital, Mandalay, is the second largest city in Myanmar. [13]

The study area included four of townships in the Mandalay region (Amarapura, Patheingyi, Tada-U and Wundwin) where the prevalence of LF had been historically high. [3, 14] Patheingyi and Amarapura lie on the outskirts of Mandalay City, whilst Tada-U and Wundwin, are located more rurally to the south. Amarapura, Patheingyi and parts of Tada-U Township lie close to the Irrawaddy River and its tributaries, whilst the Samon River passes through Wundwin. Amarapura also lies adjacent to the large Taung Tha Man Lake. A map of the study area is presented in Dickson et al. 2018.[9]

Study design

A cross-sectional household survey was conducted between February and March 2015 to assess the prevalence of LF infection and disease, participation in the MDA program, and risk factors for LF and never taking MDA. The study methodology has been reported previously alongside the results for LF prevalence and MDA participation.[9]

In brief, a two-stage random cluster sampling method was used to select households from 24 villages across the four townships. Consenting household members were screened for LF infection, examined for LF-related morbidity and completed a risk-factor questionnaire.

Infection screening. Individuals one year and older were tested for circulating filarial antigen (CFA) (signifying current infection) using Binax Now Filariasis Immunochromatographic test (ICT) cards (Alere Inc, MA, USA) on finger-prick blood samples. Individuals who were antigen positive had a further 60μL of finger prick blood taken between 2200 and 0200 and applied to duplicate microscope slides using the three-line technique to assess for microfilaraemia (Mf).

Clinical examination. Under the supervision of medical doctors, trained health workers examined participants aged 15 years and older for the presence of acute and chronic filariasis-related morbidity. Suspected cases of hydrocoele were confirmed using ultrasound (Sonosite M-Turbo, Washington, USA).

Risk factor questionnaire and GPS mapping. A pre-coded questionnaire was used to assess participation in the MDA program, as well as factors associated with LF infection, disease and never- taking MDA. Prior to data collection, the questionnaire was translated into Myanmar Language (Burmese) and pre-tested with staff of the Vector Borne Disease Control Unit. Trained health workers completed a brief

questionnaire with each participant (Additional file 1) followed by a more detailed questionnaire with the household head (Additional file 2). Direct observation was used to verify respondent answers where possible. A global positioning device was used to record the location and elevation of each household.

Data analysis

Independent variables. Data was collected on paper forms in Myanmar language (Burmese) and entered into Excel format before transfer to STATA. The distance between households and large bodies of water was calculated in ArcMap 10.5 (ESRI, Redlands, CA). An electronic map of inland water bodies in shapefile format was obtained from Global Administrative Areas database (http://www.gadm.org/country). The distance between households and water bodies was then calculated using the Near function of the Proximity Tool. The shortest distance was determined using planar (flat earth) method. An LF knowledge score was created from survey questions to assess the relationship between knowledge of LF and MDA participation. Participants received a point each if they had heard of LF and then if they correctly identified LF's mode of transmission, symptoms and treatment, giving a maximum possible score of four points.

Univariate analyses. Statistical analysis was completed using STATA version 14.2 (STATA Corporation, Texas, USA). First, a series of univariate analyses were completed to assess the association between potential risk factors for each of the three outcomes: infection (CFA positive), LF related-hydrocoele, and never taking MDA medication. A risk factor analysis for lymphoedema could not be undertaken as no cases were identified in the sample. Microfilaria positivity was not included as an outcome variable because there were a small number of Mf positive individuals and the results were collinear with CFA positivity.

The 'svy' prefix command was used to adjust for clustering effect and weight for sampling probability. T-tests, χ^2 and logistic regression were used to compare variables and generate odds-ratios adjusted for survey design. Independent variables with a p-value less than 0.2 were included in the multivariate analysis. Circulating Filarial Antigen positivity and hydrocoele demonstrated a linear association with age, so age by year was used. In contrast, the association between MDA non-participation and age had a bimodal distribution, so age by quintile was used. Total household income data demonstrated a skewed distribution, so the log of income was used to normalise its distribution. **Multivariate analyses.** Next, separate backward multivariate logistic regression analyses were completed for each of the three outcomes with and without adjustment for survey design. The variable 'Township' was added at the end of the analyses to assess whether there were additional unmeasured fixed effects associated with township that had not been accounted for. Risk factors with a p-value of less than 0.05 were considered significant. Participants with incomplete data were excluded from analyses.

Results

Characteristics of the study population

Demographics. A total of 450 households in 24 villages were sampled. Of those, 20 households (4.4%) were excluded: 15 were absent and five declined to participate. From the remaining 430 households, 1014 individuals participated in the study. The median age of participants was 36 years (interquartile range (IQR): 30, range: 1–86). Significantly more females than males were included in the sample (63.7% vs 36.3%, $p < 0.001$) with no significant difference in age between genders. The median number of inhabitants per household was four (IQR: 3, range: 1–12) with an average household monthly income of 120,000 Myanmar Kyat (85 USD) IQR: 120,000, range: 5,000 to 1,500,000).

Infection prevalence. Forty-six of the 1001 participants tested for infection by CFA were positive (crude prevalence: 4.6%, adjusted for age, gender and survey design: 2.63%). The median age of infected individuals was 46 years (IQR: 23, range 8–81 years). A cluster of five villages in Amarapura and Tada-U townships had a notably higher prevalence of infection compared to the remaining villages (mean 13.32% vs 1.14%). Microfilariae were found in 39.02% of antigen positive individuals, representing an overall adjusted Mf prevalence estimate of 1.03% (assuming all antigen negative persons were also Mf negative).

Hydrocoele prevalence. Fifteen of the 269 men aged over 15 who were examined had an LF-related hydrocoele (crude prevalence 5.58%, adjusted for age and survey design 2.78%). The median age of males suffering from an LF-related hydrocoele was 55 years (IQR: 12, range: 48–71 years). The highest prevalence occurred in three villages in Amarapura Township where prevalence ranged from 21.53 to 36.81%.

MDA program participation. Ninety-five percent of households reported ever being visited by the MDA program. Of these, the mean number of visits was 2.59. Ninety percent of household members reported being present during the last MDA round in 2014. Eighty percent of participants reported taking MDA medication at least once – in other words, 20% were systematic non-takers. Of those who had ever taken MDA, the mean number of times medication had been consumed was 2.73. Ten percent of participants had actively declined to take MDA medication (despite it being offered) on at least one occasion. The most common reasons reported were a fear of side effects and a perception that co-morbidities were a contraindication.

Risk factors for LF infection

Table 1 outlines the univariate analysis of factors associated with LF infection (by CFA) adjusted for survey design (i.e. weighted for sampling probability and adjusted for clustering). Infection was positively associated with age (by year), male gender, household monthly income, residing in Amarapura township, the absence of screens/glass on household windows, the number of people per household room and having moved to one's current village. Infection was also positively associated with never taking MDA medication as well as not taking it in the last year. Infection was negatively associated with elevation (per metre) and distance to the nearest body of water (per km).

The association of infection with number of times MDA was taken was complex and non-intuitive. Compared to those who had never taken MDA, decreasing infection prevalence was only observed in those who took MDA a few or intermediate number of times (Table 1). Prevalence was higher in those who took the MDA 5 or 6 times. All of the participants with infection who reported taking 5 to 6 rounds of MDA resided in Amarapura, the highest prevalence township (Additional file 3) and thus may have been more intensively targeted, potentially more likely to be reinfected, or more familiar with MDA and possibly more likely to give responses showing social desirability bias.

Table 2 demonstrates the factors significantly associated with LF infection following unadjusted and adjusted multivariate logistic regression. Forty-nine of the 1001 participants tested for infection were excluded from the final multivariate model due to missing data. Prior to adjustment, infection was positively associated with age (per year), male gender, never having taken MDA medication, the absence of screens/glass on windows and the number of people per household room. Infection was negatively associated with elevation (per metre). After adjustment, all variables except never having taken MDA medication and the absence of screens/glass on windows remained significant.

Table 1
Univariate logistic regression analysis of association between infection (measured by CFAa) and individual/ household risk factors; weighted and adjusted for survey design (n = 1001)

Risk Factor	Total (n)	CFA positive (%)[b]	CFA positive		
			aOR[b]	95% CI[c]	p-value
Individual Risk Factors					
Age (per year)	997	–	1.03	1.01–1.05	0.011
Gender	1001				
Male	365	4.76	2.34	1.03–5.36	0.044
Female	636	2.09			
Occupation	975				
None/home duties	257	2.84	1.01	0.27–3.82	*0.985*
Student	160	0.78	0.27	0.02–3.20	*0.286*
Manual labour	519	4.00	1.45	0.35–5.97	*0.596*
Other (ref)	39	2.80			
Work environment	947				
Outdoor	325	3.26	1.08	0.47–2.47	*0.853*
Indoor or mixed	622	3.03			
Moved to current village	992				
Yes	148	8.13	3.46	1.45–8.25	0.007
No	844	2.49			
Slept under a bed-net last night	996				
Yes	907	2.75	0.46	0.10–2.07	*0.298*
No	89	5.76			
Never taken MDA medication	994				
Yes	188	7.55	3.67	1.51–8.93	0.006
No	806	2.18			
No. times MDA taken	985	–	0.78	0.57–1.08	*0.133*
0 (ref)	188	7.55			

Risk Factor	Total (n)	CFA positive (%)[b]	CFA positive		
1–2	336	2.92	0.37	0.12–1.16	*0.085*
3–4	273	0.57	0.07	0.01–0.37	0.003
5–6	188	4.40	0.56	0.20–1.62	*0.273*
Did not take MDA last year	994				
Yes	237	7.18	3.80	1.57–9.17	0.005
No	757	2.00			
Household Risk Factors					
Township	1001				
Amarapura	297	9.07	9.96	2.98–33.29	0.001
Patheingyi	113	2.61	2.68	0.24–29.54	*0.405*
Tada-U	267	3.38	3.49	0.87–13.94	*0.075*
Wundwin (ref)	324	0.99			
Log household monthly income	965	–	1.89	1.30–2.75	0.002
Highest level of education	993				
None/primary	325	3.38	7.44	0.82–67.34	*0.072*
Secondary	528	3.81	8.43	0.95–74.90	*0.055*
Tertiary (ref)	140	0.47	1.00		
Elevation (by metre)	997	–	0.95	0.92–0.99	0.011
Distance to nearest water body (per km)	989	–	0.91	0.85–0.98	0.011
No screens or glass on windows	994				
Yes	373	6.43	3.52	1.32–9.44	0.015
No	621	1.92			
Number of people in household	997	–	1.24	0.96–1.60	*0.092*
No. people per bednet (ratio)	987	–	1.23	0.99–1.53	*0.065*

Risk Factor	Total (n)	CFA positive (%)[b]	CFA positive		
No. of people per room (ratio)	965	–	1.60	1.35–1.89	0.000

*[a]Circulating Filarial Antigen [b]Adjusted for survey design [c]95% Confidence interval *No CFA positive individuals.*

Table 2
Multivariate logistic regression analysis of association between infection (measured by CFAa) and individual/household risk factors; with and without adjustment for survey design (n = 952)

Risk Factor	Adjusted for covariates			Adjusted for covariates and survey design		
	OR	95% CI[b]	p-value	aOR[c]	95% CI	p-value
Individual Risk Factors						
Age (per year)	1.03	1.01–1.05	0.001	1.03	1.01–1.06	0.002
Male gender	2.31	1.19–4.51	0.014	3.11	1.23–7.87	0.019
Never taken MDA medication	2.02	1.01–4.04	0.045	2.09	0.70–6.22	*0.177*
Household Risk Factors						
Elevation (metre)	0.97	0.95–0.99	0.001	0.97	0.94–1.00	0.023
No screens or glass on windows	2.12	1.02–4.43	0.045	1.23	0.41–3.72	*0.703*
No. of people per room (ratio)	1.30	1.07–1.59	0.009	1.56	1.26–1.93	0.000

[a]Circulating Filarial Antigen [b]95% Confidence interval [c]Adjusted for survey design

Risk factors for LF-related hydrocoele

Table 3 shows the univariate association between LF-related hydrocoele and potential risk factors. Hydrocoele was positively associated with age (by year) and residing in Amarapura Township, and negatively associated with working in an outdoor environment. A relationship between hydrocoele, frequency of bathing and shoe wearing was hypothesised; however there was insufficient variance in responses to assess the association.

Table 4 summarises the significant factors associated with LF-related hydrocoele following multivariate logistic regression. All but one of the 269 men examined for hydrocoele were included in the multivariate model. Prior to adjustment, hydrocoele was positively associated with age (by year), infection (by CFA) and residing in Amarapura Township. Following adjustment, the association with infection lost significance whilst the other two variables did not.

Table 3
Univariate logistic regression analysis of association between LF-related hydrocoele and individual/household risk factors; weighted and adjusted for survey design (n = 269)

Risk Factor	Total	Proportion with Hydrocoele (%)[a]	Hydrocoele present		
			aOR[a]	95% CI[b]	p-value
Individual Risk Factors					
Age (by year)	268	–	1.05	1.03–1.08	0.000
Occupation	265				
None/home duties	32	10.45	1.85	0.17–2.82	*0.603*
Student	2	0	–		
Manual labour	213	3.32	0.54	0.04–6.89	*0.625*
Other (ref)	18	5.93	1.00		
Work environment	258				
Outdoor	145	0.85	0.20[c]	0.05–0.72	0.014
Indoor or mixed	113	7.29			
Moved to current village of residence	268				
Yes	42	7.68	2.14	0.45–10.24	*0.327*
No	226	3.75			
CFA[d] positive	269				
Yes	19	12.25	3.65	0.81–16.38	*0.088*
No	250	3.69			
Microfilariae positive[e]	266				
Yes	7	18.18	5.39	0.83–35.04	*0.076*
No	259	3.96			
Never taken MDA medication	269				
Yes	56	4.66	1.15	0.22–5.98	*0.859*

Risk Factor	Total	Proportion with Hydrocoele (%)[a]	Hydrocoele present		
No	213	4.07			
Household Risk Factors					
Township	269				
Amarapura	59	13.92	11.12	1.85–66.89	0.011
Patheingyi	27	8.02	5.98	0.40–89.48	*0.184*
Tada-U	64	1.73	1.21	0.08–17.21	*0.884*
Wundwin (ref)	119	1.44	1.00		
Log household monthly income			1.43	0.77–2.64	*0.241*
Highest HH Education	268				
None/Primary	81	2.74	0.26	0.03–2.78	*0.253*
Secondary	150	3.29	0.32	0.04–2.41	*0.253*
Tertiary (ref)	37	9.72	1.00		
Drinking water type (by WHO classification)	268	–	1.01	0.41–2.47	*0.981*
Sanitation type (by WHO classification)	269	–	0.26	0.04–1.63	*0.143*
Elevation (by metre)	269	–	0.98	0.96–1.01	*0.148*
Distance to nearest water body (per km)	267	–	0.95	0.89–1.01	*0.075*
No. of people per HH room (ratio)	259	–	1.35	0.92–1.98	*0.116*

[a]Adjusted for survey design [b]95% Confidence interval [c]unadjusted values given due to study stratum with single sampling unit [d]Circulating Filarial Antigen [e]All CFA negative individuals assumed to be microfilariae negative

Table 4
Multivariate logistic regression analysis of association between LF-related hydrocoele and individual/household risk factors; with and without adjusted for survey design (n = 268)

Risk Factor	Adjusted for covariates			Adjusted for covariates and survey design		
	OR	95% CI[a]	p-value	aOR[b]	95% CI	p-value
Individual Risk Factors						
Age (by year)	1.05	1.01–1.10	0.018	1.06	1.02–1.09	0.001
CFA positive	5.49	1.47–20.5	0.011	1.34	0.23–7.92	*0.739*
Household Risk Factors						
Township						
Amarapura	8.45	1.69–42.34	0.009	8.56	1.33–55.22	0.026
Patheingyi	2.33	0.19–28.24	*0.506*	7.85	0.43–145.09	*0.158*
Tada-U	0.98	0.08–11.76	*0.988*	1.50	0.10–21.68	*0.755*
Wundwin (ref)	1.00			1.00		

[a] 95% Confidence interval [b] Adjusted for survey design

Risk factors for non-participation in the MDA program

Table 5 shows the univariate analysis of potential factors associated with never taking MDA medication, adjusted for survey design. Never taking MDA was positively associated with male gender, moving to one's current village, declining offered MDA medication, residing in Amarapura and Tada-U Townships and the number of people per household room. Never taking medication was negatively associated with knowledge of LF, being visited by the MDA program and the number of times visited. Since non-participation was greater in those who declined medication and had a lower knowledge of LF, a side analysis of the relationship between these two independent variables was conducted. Declining offered medication was significantly less likely in those with greater LF knowledge (OR 0.68, p = 0.025).

Table 6 illustrates the factors significantly associated with never taking MDA following multivariate analysis, without and with adjustment for survey design. Of the 1007 participants who self-reported MDA participation, 163 were excluded from the final multivariate model as a result of missing data. Prior to adjustment, systematic non-participation was positively associated with extremes of age (less than 15 years and 60 years or older), male gender, ever declining MDA medication and residing in Amarapura Township. It was negatively associated with LF knowledge, the number of visits by the MDA program and the proportion of household members present during the last MDA. Following adjustment for survey design, the association with LF knowledge, and number of LF program visits lost significance whilst the association with moving to one's current village became significant.

Table 5
Univariate logistic regression analysis of association between never having taken MDA medication and individual/household risk factors; weighted and adjusted for survey design (n = 1007).

Risk Factor	Total (n)	Proportion that had never taken MDA medication (%)	Never taken MDA medication		
			aOR[a]	95% CI[b]	p-value
Individual Risk Factors					
Age group (year)	1003				
0–14	177	18.36	0.77	0.33–1.78	*0.527*
15–29	201	20.69	0.90	0.38–2.09	*0.788*
30–44	273	13.10	0.52	0.24–1.13	*0.092*
45–59	221	13.64	0.54	0.21–1.41	*0.198*
60+ (ref)	131	22.57	1.00		
Gender	1007				
Male	366	21.31	1.61	1.10–2.35	0.017
Female	641	14.43			
Occupation	986				
None/home duties	263	15.61	0.55	0.20–1.53	*0.241*
Student	163	17.29	0.63	0.17–2.36	*0.472*
Manual labour	520	16.86	0.61	0.23–1.59	*0.296*
Other (ref)	40	25.04	1.00		
Moved to their current village of residence	1000				
Yes	146	27.96	2.08	1.06–4.07	0.034
No	854	15.74			
Ever declined MDA medication	935				

Risk Factor	Total (n)	Proportion that had never taken MDA medication (%)	Never taken MDA medication		
Yes	74	52.36	9.18	2.43–34.65	0.002
No	861	10.70			
Household Risk Factors					
Township	1007				
Amarapura	304	20.22	1.81	1.08–3.03	0.027
Patheingyi	111	20.29	1.82	0.37–8.80	*0.443*
Tada-U	268	20.52	1.84	1.10–3.08	0.022
Wundwin (ref)	324	12.30	1.00		
Log household monthly income	970	–	1.52	0.99–2.34	*0.055*
Highest level of education	999				
None/primary	326	16.83	1.91	0.76–4.82	*0.163*
Secondary	531	19.75	2.32	0.85–6.31	*0.095*
Tertiary (ref)	142	9.59	1.00		
Literacy of household head	994				
Illilterate	84	15.18	0.87	0.34–2.21	*0.751*
Partially literate	54	22.64	1.41	0.55–3.67	*0.460*
Literate	856	17.15	1.00		
Knowledge of LF (by score, n of 4)	959	–	0.66	0.46–0.94	0.024
Visited by MDA program	997				
Yes	939	14.30	0.07	0.03–0.18	0.000
No	58	69.30			

Risk Factor	Total (n)	Proportion that had never taken MDA medication (%)	Never taken MDA medication		
Total number of MDA program visits (by n of 6)	961	–	0.49	0.33–0.73	0.001
Proportion of household present during last MDA (ratio)	900	–	0.28	0.06–1.34	*0.107*
No. of people per room (ratio)	970	–	1.22	1.04–1.43	0.017

[a]Adjusted for survey design [b]95% Confidence interval

Table 6
Multivariate logistic regression analysis of association between never having taken MDA medication and individual/household risk factors; weighted and adjusted for survey design (n = 844).

Risk Factor	Adjusted for covariates			Adjusted for covariates and survey design		
	OR	95% CI[a]	p-value	aOR[b]	95% CI	p-value
Individual Risk Factors						
Age group (year)						
0–14	2.59	1.31–5.13	0.006	2.89	1.11–7.51	0.031
15–29	1.61	0.82–3.15	*0.165*	1.72	0.83–3.57	*0.139*
30–44 (ref)	1.00			1.00		
45–59	1.74	0.91–3.30	*0.092*	1.30	0.65–2.59	*0.438*
60+	3.00	1.47–6.11	0.003	4.00	1.53–10.48	0.007
Male gender	1.64	1.07–2.51	0.024	1.85	1.05–3.25	0.035
Moved to current village of residence	1.53	0.86–2.71	*0.148*	2.84	1.15–7.02	0.026
Ever declined MDA medication	6.90	3.49–13.63	0.000	13.76	4.79–39.58	0.000
Household Risk Factors						
Township						
Amarapura	2.92	1.68–5.05	0.000	2.99	1.39–6.43	0.007
Patheingyi	0.87	0.40–1.92	*0.737*	2.04	0.70–6.00	*0.184*
Tada-U	0.56	0.30–1.05	*0.072*	0.47	0.20–1.10	*0.078*
Wundwin (ref)				1.00		
Knowledge of LF (by score, n of 4)	0.80	0.64–1.00	0.048	0.77	0.49–1.21	*0.248*
Total number of MDA program visits (by n of 6)	0.72	0.61–0.85	0.000	0.70	0.47–1.03	*0.069*

Risk Factor	Adjusted for covariates			Adjusted for covariates and survey design		
Proportion of household present during last MDA (by ratio)	0.24	0.10–0.57	0.001	0.18	0.04–0.96	0.045

[a] 95% Confidence interval [b] Adjusted for survey design

Discussion

This study has been the first to examine risk factors related to LF and MDA participation in Myanmar. It assessed three outcomes in an area with ongoing transmission after six rounds of MDA including: persistent infection (measured by CFA), never having taken MDA medication and LF-related hydrocoele. It found that persistent infection was related to both baseline (pre-MDA) factors and low uptake of MDA medication. Never taking MDA medication, in turn, was associated with both program reach and individual compliance factors. Finally, LF-related hydrocoele was significantly associated with increasing age and residing in the historically endemic township of Amarapura.

Despite six rounds of MDA, infection remained significantly associated with baseline risk factors, which include host characteristics and exposure to infected vectors. The relationship between infection and increasing age found in this study is well established.[15] It is thought to relate to both increasing exposure to infected mosquitoes with age and the inefficient transmission of L3 larval stages from mosquitoes to humans.[16]

The higher prevalence of LF infection amongst males found here is also well documented.[15, 17] Historically, it was suggested that this was the result of greater occupational exposure. However, the persistence of male predominance, following adjustment for occupation, outdoor-work and MDA participation in this analysis, supports the hypothesis that there is also a biological basis for this difference.[18–20]

Risk of infection was strongly associated with the number of people per household room, a marker of crowding. Entomological studies have shown that rooms with more inhabitants have an increased density of indoor *Culex* mosquitoes.[21] It is therefore hypothesised that crowding may lead to greater density of indoor *Culex* mosquitoes increasing transmission risk amongst household members. Efforts to reduce overcrowding, which are employed for other communicable diseases, may therefore also decrease LF transmission. Whilst a relationship between crowding and infection has not previously been documented, a link has been observed between household size and infection in children in Brazil, where *Culex* is also the vector.[22] When crowding was replaced by household size in our final model, there was a positive association, but it did not reach significance ($p = 0.058$, results not shown). This suggests that household size, as well as density, may predispose to infection in *Culex* regions, but this requires further investigation.

The absence of screens or glass on household windows was also associated with higher infection risk but lost significance following adjustment for survey design. This may be due to sample heterogeneity, and that Amarapura Township had both a high infection prevalence and low number of screens/glass on windows. The relationship is nonetheless noteworthy, because studies in Africa have shown that windows and doors are the preferred entry point for *Culex* mosquitoes, and the addition of screens reduces their indoor density.[23, 24] Other variables related to night-time vector exposure, including bed-net ownership and usage, also showed a protective association, but did not reach significance. This was probably because bed-net ownership and usage were uniformly high across the study area. Together, this suggests that individuals may have been infected whilst in their household but outside of their bed-net. The addition of screens to household windows could therefore be an effective intervention to reduce the LF transmission and deserves further study and trials.

An interesting finding was the association between small changes in elevation and infection risk. Whilst a negative association between elevation and infection risk is well documented, this typically occurs with larger variations in altitude.[25, 26] This is because at higher altitudes, atmospheric temperatures decrease, resulting in reduced mosquito survival and slower parasite development within the vector.[27] In this area, which is located within the central plains of Myanmar, altitude only ranged between 45 and 269 metres above sea level. This would be insufficient to affect vector survival, but instead, indicates low-lying households that may be closer to bodies of water. The distance from households to large bodies of water was also directly measured. Whilst significant in the univariate analysis, the variable lost significance when it replaced or was added alongside elevation in the final model. This could be because elevation more accurately captured subtle proximity to water such as smaller waterways, areas prone to flooding, or households closest to water along a riverbank. These findings support earlier work in demonstrating the usefulness of elevation as an indirect marker for proximity to water and therefore infection risk in low-lying contexts.[28]

A significant finding in this study was the strong association between persistent infection and never taking MDA. Whilst the relationship lost significance after adjustment, possibly due to the clustering of non-participation, it retained a strong positive effect (OR 2.09). This relationship is explained by both the mechanisms with which MDA medications control LF at the individual and community levels. The predominant effect of MDA is microfilaricidal, thereby reducing local transmission and the chance of new infection.[29] This is reflected in the study area, where villages with greater than 65 percent MDA participation, had a mean CFA prevalence of 2.08%, compared to 9.76% in villages with lesser participation. The secondary effect is macrofilaricidal, reducing the burden of adult worms and therefore eventually CFA.[30] At the individual level, this explains the lower weighted and adjusted prevalence in those who had participated in the MDA program (1.60%) compared to those who had not (6.74%). The high prevalence of infection amongst ‘systematic non-takers’ supports studies elsewhere in highlighting their significant role as a reservoir for ongoing transmission in the community.[31, 32]

Understanding the causes of MDA non-participation, especially systematic non-taking, are therefore crucial to improving control efforts. In the study area, non-participation was related to both programmatic

reach (the proportion of targeted persons who are offered medication) and individual compliance (the proportion who take the offered medication).

The programmatic factors associated with non-participation suggest households were either not visited by the program, or the members of the household were absent at the time of the visit. While almost all (95%) of surveyed households reported being visited by the MDA program at least once, the mean number of visits was only 2.59, with fewer visits predictive of never having taken MDA. In the households that were visited, absenteeism further predisposed to non-participation. The likelihood of never taking MDA was lower in persons from households with fewer members present during the last round, and in persons that had migrated from another village. The lower medication uptake in males may also have related to absenteeism, since we found that during daytime data collection men were often away working.

These findings corroborate those of Linn et al. who recently conducted a qualitative survey on barriers to MDA participation in Myanmar (unpublished).[33] They interviewed members of the community and National Program to Eliminate LF (NPELF) in three townships with persistent transmission in Mandalay, and the adjacent Magway and Sagaing Regions. They found community members were often unaware of previous rounds, suggesting they may have been missed. Of those who were aware of the previous rounds, a number stated they had not received medication because they were away. Meanwhile drug distributors reported that financial, human resource and time limitations prevented them from fulfilling their duties and mopping-up recipients who were initially missed. The NPELF should therefore ensure that future rounds reach all households, are sufficiently resourced and conducted at a time when household members are likely to be present. A strong emphasis should also be made to mop-up eligible recipients who were missed during the initial round.

In addition to programmatic reach, our results indicate that individual compliance was a contributing factor to overall MDA uptake. The strong association between ever declining medication and systematic non-participation suggests that a significant proportion of non-participators were offered medication but did not take it. The most common reasons reported in both our study and Linn et al. were fear of side effects or a perception that co-morbidities were a contraindication.[33] Although adverse events are rare, community concern has hampered MDA in many countries and resulted in the postponement of the 2006 MDA round in Mandalay Region.[3] The lower participation in the extremes of age may also have related to fears over side effects. Older age groups have greater co-morbidities and therefore are more likely to have perceived that the medication was contra-indicated. Linn et al. also found the elderly were concerned that the medications would worsen existing dizziness.[33] Meanwhile in children, lower participation has been attributed to parents withholding medication due to concerns over potential adverse effects.[11]

Education initiatives regarding LF, the MDA program and common misconceptions have been effective in improving MDA compliance.[34–36] These studies reported that greater LF knowledge reduced the likelihood of declining medication and non-participation, suggesting that these interventions would likely

also be effective in Myanmar. The NPELF should consider efforts to improve community education and dispel myths in order to improve MDA participation.

Amarapura had significantly lower levels of MDA participation compared to the other townships in the study. Douglass et al. similarly found low participation in young people surveyed there in 2013 and 2014.[10] This lower participation could not be accounted for by the programmatic reach and compliance factors assessed. Of the four townships, Amarapura is the most urban and had the highest average household income. Studies elsewhere have found that MDA participation can be more difficult to achieve in urban areas because of a lack of urban strategy, fewer peripheral health workers, poor health care infrastructure, the presence of unorganised settlements and large numbers of migrants.[11] Compared to other townships, Amarapura had the highest proportion of individuals who had moved from another village but a similar ratio of household members present during the last round and the highest number of NPELF visits. Within urban areas, studies have also found that higher income individuals can be harder to reach in surveys and are more likely to decline to participate in MDA programs.[11] Amarapura had the lowest proportion of individuals who reported declining MDA medication. When income was assessed in a subgroup analysis of the township, however, there was a trend toward lower participation with higher income but it did not reach significance (cOR 1.07 $p = 0.642$, aOR 1.41 $p = 0.080$). The lower participation levels in Amarapura, therefore, may relate to its urban location, more mobile population and higher incomes, but this requires further analysis.

In addition to exploring causes for persistent infection and MDA non-participation, this study also assessed risk factors for LF-related hydrocoele. The positive association found between age and hydrocoele has been well documented.[15] This is thought to be due to the progressive onset of lymphatic dysfunction with chronic filarial infection.[37] Hydrocoele was also found to be associated with CFA positivity but this relationship lost significance following adjustment for survey design. Since individuals with hydrocoele are often CFA negative, this association could potentially reflect an increased risk of hydrocoele development in those with chronic or recurrent infection. The higher risk of hydrocoele in Amarapura probably relates to the historically high infection prevalence there, which is not reflected in current CFA status. These findings underscore the importance of reducing infection to prevent the development of LF-related hydrocoele.

The study results reported should be interpreted in light of some limitations. Firstly, more females than males participated in the study. Whilst gender was adjusted for, it led to wider odds-ratio confidence intervals. Secondly, data was missing from a number of risk factor variables (see total column in Tables 1, 3 and 5) leading to fewer numbers of participants in the final models for infection and never-taking MDA. In addition to widening confidence intervals, it is possible this may have biased the results. Thirdly, other potential environmental factors such as rainfall, temperature and population density were not included, which may have provided a more complete explanation of risk. Lastly, local health workers and members of the NPELF assisted with data collection. It is therefore possible that participants' responses regarding MDA participation could have been biased towards 'acceptable' replies. The low levels of reported MDA participation, however, suggest this was unlikely.

The results of this study will assist Myanmar's NPELF and contribute to the global understanding of LF risk factors. Knowledge of the factors associated with persistent infection will help the National Program to better allocate its resources in elimination efforts. This should include interventions to improve MDA participation and potentially the screening of household windows and doors. In order to improve participation, our results suggest that emphasis needs to be placed both on improving reach, with particular attention to mopping-up missed participants, and compliance through educational initiatives. Since the findings reflect many common global reasons for poor MDA uptake and those of Linn et al, it is reasonable to infer that they could be generalisable to other regions of Myanmar. The identified infection risk factors may also apply to other countries where *Culex* is the vector. Finally, the identification of hydrocoele risk factors contributes to the understanding of LF morbidity and will help Myanmar to better target alleviation programs.

Conclusion

This study assessed risk factors for LF infection, disease and never-taking MDA in an area of persistent LF transmission in Myanmar. It found that persistent LF infection was linked to both baseline risk and lack of participation in the MDA program. In turn, MDA participation related to both program reach and individual compliance factors. It also identified that hydrocoele risk was higher in those who were older and residing in the historically high prevalence township of Amarapura. These results will assist the NPELF to improve its MDA rounds, and to better target its morbidity management programs.

Abbreviations

LF
Lymphatic filariasis; MDA:Mass drug adminstration; WHO:World Health Organization; NPELF:National Program to Eliminate LF; CFA:Circulating Filarial Antigen; Mf:Microfilaraemia
ICT:Immunochromatographic test; OR:Odds ratio; 95%CI:95% confidence interval; IQR:Interquartile range.

Declarations

Supporting Information

The following supporting information is available. Additional file 1: Individual participant survey in English and Myanmar language, Additonal file 2: Household survey in English and Myanmar language and Additional file 3: Unadjusted infection prevalence by number of times MDA medication taken and township.

Acknowledgements

We would like to thank all individuals who offered their time to participate in the study. We would also like to acknowledge the other individuals who assisted in data collection, in particular Dr Yi Yi Win from the Vector Borne Disease Control Unit and the staff of the four township hospitals. We are grateful to the

clinical training and advice provided by Professor Chris King and Associate Professor Daniel Tisch from Case Western Reserve University. We are very grateful to the NIH/NIAID Filariasis Research Reagent Resource Center (www.filariasiscenter.org) for providing the ICT positive control. Lastly we would like to thank Professor Susan Gordon for her assistance in study planning, logistics and data collection.

Ethics approval and consent to participate

The study was approved by The Human Research Ethics Committee, James Cook University (approval H5849) and The Ethics Review Committee on Medical Research Involving Human Subjects, Department of Medical Research, Myanmar Ministry of Health. The Ministry of Health, Regional Health Director and village leaders provided permission for this study. Written informed consent was obtained from all participants or their guardians.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

NNA, TWN, TW, and SSW were involved in Myanmar's National LF Elimination Program at the time of the study. MS works as a self-employed private general practitioner in Mandalay. He volunteered his time to assist with data collection during the study.

Funding

This study was funded by the generous support of the Australian Institute of International Affairs, Euan Crone, the College of Medicine and Dentistry of James Cook University and The Royal College of Pathologists of Australasia. BFRD was the recipient of all study funding. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

Study conception and design: BFRD, PMG; Study planning: BFRD, PMG, NNA, TWN, TW, SSW. Data collection: BFRD, PMG, TWN, TW, SSW, MS, JD; Mapping and geospatial analysis: PW, KW; Data analysis: BFRD, PMG. Drafting of manuscript: BFRD, PMG. All authors reviewed and approved the final manuscript.

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