

# 

**Citation:** Gunaratna IE, Chandrasena NTGA, Vallipuranathan M, Premaratna R, Ediriweera D, de Silva NR (2024) The impact of the National Programme to Eliminate Lymphatic Filariasis on filariasis morbidity in Sri Lanka: Comparison of current status with retrospective data following the elimination of lymphatic filariasis as a public health problem. PLoS Negl Trop Dis 18(8): e0012343. https://doi.org/10.1371/journal.pntd.0012343

Editor: Wilma A. Stolk, Erasmus MC, NETHERLANDS, KINGDOM OF THE

Received: December 24, 2023

Accepted: July 6, 2024

Published: August 14, 2024

**Peer Review History:** PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pntd.0012343

**Copyright:** © 2024 Gunaratna et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

RESEARCH ARTICLE

The impact of the National Programme to Eliminate Lymphatic Filariasis on filariasis morbidity in Sri Lanka: Comparison of current status with retrospective data following the elimination of lymphatic filariasis as a public health problem

# Indeewarie E Gunaratna<sup>1</sup>, Nilmini T. G. A Chandrasena<sup>2\*</sup>, Murali Vallipuranathan<sup>1</sup>, Ranjan Premaratna<sup>3</sup>, Dileepa Ediriweera<sup>4</sup>, Nilanthi R de Silva<sup>2</sup>

1 Anti Filariasis Campaign, Ministry of Health, Colombo, Sri Lanka, 2 Department of Parasitology, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka, 3 Department of Medicine, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka, 4 Health Data Science Unit, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka, 4 Health Data Science Unit, Faculty of Medicine, University of Kelaniya, Sri Lanka

\* nilmini@kln.ac.lk

# Abstract

# Introduction

Sri Lanka implemented the National Programme for Elimination of Lymphatic Filariasis (NPELF) in its endemic regions in 2002. Five annual rounds of mass drug administration using the two-drug combination diethylcarbamazine (DEC) and albendazole led to sustained reductions in infection rates below threshold levels. In 2016, WHO validated that Sri Lanka eliminated lymphatic filariasis as a public health problem.

# Objective

To explore the impact of the NPELF on lymphatic filariasis morbidity in Sri Lanka.

# Methods

Passive Case Detection (PCD) data maintained in filaria clinic registries from 2006–2022 for lymphoedema and hospital admission data for managing hydroceles/spermatoceles from 2007–2022 were analyzed. The morbidity status in 2022 and trends in overall and district-wise PCD rates were assessed. Poisson log-linear models were used to assess the trends in PCD for endemic regions, including district-wise trends and hospital admissions for the management of hydroceles/spermatoceles.

# Results

In 2022, there were 566 new lymphoedema case visits. The mean (SD) age was 53.9 (16.0) years. The staging was done for 94% of cases, of which 79% were in the early stages

Data Availability Statement: All relevant data are included in the manuscript. In addition the current data (2022 and 2023) may be accessed via the Annual Health Bulletin of AFC ;https://afc.health.gov.lk/annual-reports-health-bulletin/ at the AFC website, https://afc.health.gov.lk/.

**Funding:** The author(s) received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

(57.3% and 21.4% in stages two and one, respectively). Western Province had the highest caseload (52%), followed by the Southern (32%) and Northwestern (16%) Provinces, respectively. The reported lymphoedema PCD rate in 2022 was 0.61 per 10,000 endemic population. The overall PCD rate showed a decline of 7.6% (95%CI: 4.9% - 10.3%) per year (P < 0.0001) from 2007 to 2022. A steady decline was observed in Colombo, Gampaha and Kurunegala districts, while Kalutara remained static and other districts showed a decline in recent years. Further, admissions for inpatient management of hydroceles/spermatoceles showed a declining trend after 2015.

# Conclusions

The PCD rates of lymphoedema and hydroceles/spermatoceles showed a declining trend in Sri Lanka after the implementation of the NPELF.

# Author summary

In the year 2000, the World Health Organization initiated the mass drug administration program to eliminate lymphatic filariasis. Sri Lanka implemented the program for five years (2002–2006), offering yearly single doses of anti-filarial treatment to the eligible population of all eight endemic districts. In 2016, Sri Lanka was acknowledged as having eliminated lymphatic filariasis as a public health problem. This study explored the impact of the mass drug administration program on lymphoedema and hydrocele/spermatoceles passive case detection rates using filaria clinic and hospital admission data. A reduction in new lymphoedema case visits to filaria clinics and hospital admissions for hydrocele/spermatoceles management was noted two decades after implementing mass anti-filarial treatment in Sri Lanka.

# Introduction

Lymphatic filariasis (LF), ranked as one of the world's leading causes of permanent and longterm disability, is targeted for global elimination [1,2]. The causative nematodes, Wuchereria bancrofti, Brugia malayi and B. timori dwell within the lymphatic system (distal lymphatics and lymph nodes) and impair lymph drainage, causing severely disabling chronic manifestations, lymphoedema and its severe form elephantiasis of the legs and hands and hydrocoele [3]. In bancroftian filariasis, lymphoedema and elephantiasis commonly affect the lower legs and thighs, while less commonly, other sites such as arms, scrotum, penis, vulva, and breasts are affected, whereas in *B. malayi* infections, the lymphoedema is confined to below the knees and genito urinary manifestations such as hydrocoele and chyluria are a rarity [4]. Considering the huge socioeconomic burden of LF along with advances in diagnostics and treatment, the World Health Assembly in 1997 resolved to eliminate LF as a public health problem [5]. Subsequently, the World Health Organization launched the Global Programme to Eliminate LF in the year 2000 based on twin strategies: annual mass drug administration (MDA) to all at-risk populations and managing morbidity and preventing disability (MMDP) [6]. In the roadmap for eliminating neglected tropical diseases (NTDs), the global elimination of LF as a public health problem is targeted for 2030 [7].

In line with the global initiative, Sri Lanka's National Programme for Elimination of Lymphatic Filariasis (NPELF) was implemented in 2002 in the eight endemic districts: Colombo, Gampaha and Kalutara of Western Province, Galle, Matara and Hambantota of Southern Province and Kurunegala and Puttalam of Northwestern Province. Bancroftian filariasis was highly endemic in the densely populated towns of Colombo, Galle and Matara, where unplanned urbanization and coconut coir industry in Galle and Matara provided abundant breeding sites for the principal vector *Culex quinquefasciatus* while brugian filariasis was considered eliminated at that time [8]. Five annual rounds of MDAs using DEC and albendazole were administered in the endemic region from 2002–2006. MMDP services were provided to the diseased via a network of filaria clinics. In 2016, Sri Lanka was declared to have eliminated LF as a public health problem after meeting all the criteria stipulated by the WHO to verify elimination [9].

Since initiating the national elimination program, the LF infection parameters have shown a steady decline. The overall microfilaria (MF) rate, which was 0.2% in 2001, before the launch of the NPELF, was down to 0.06% in 2016, at the time of declaration of elimination as a public health problem and is 0.03% at present [8]. Thus, two decades following the elimination drive, the percentage reduction of microfilaraemia was 80%. The vector infection and infective rates have declined to 0.49% and 0.03%, respectively [10]. A limited number of studies have been conducted to date in Sri Lanka to examine the impact of the NPELF on chronic LF morbidity states (lymphoedema and hydrocoele) [11,12]. Worldwide, few have examined the impact of MDA from a clinical perspective, and reports are inconsistent [13].

At present, Sri Lanka is in the LF post-validation surveillance phase with its main objective of reducing the reservoir of residual infections in the population, which involves detecting, mapping and treating MF carriers to reduce the risk of transmission and prevent the re-establishment of infection. Thus, priority is given to parasitological and entomological surveillance. The nationwide burden of LF morbidity has never been assessed, and no active disease surveillance program exists. However, the network of filaria clinics scattered within the endemic regions maintains registries of patients who present directly or are referred for lymphoedema management. These filaria clinics provide the basic morbidity care package which includes advice and demonstration on the significance of daily washing of the affected areas in the prevention of Acute Dermato-Lymphangio-Adenitis (ADLA), patient education on skincare and hygiene, provision of recommended antibacterials and antiseptics to minimize the ADLA episodes triggering the progression of lymphoedema and promotion of measures to improve lymph drainage (compression, elevation and exercises) [14]. The MMDP services in Sri Lanka do not encompass tertiary care (rehabilitation, psychological and social support).

Patients with hydroceles rarely visit the filaria clinics as these clinics are not equipped to provide surgical services. Thus, data on hydrocele cases are rarely documented in the filaria clinic registries; however, government hospital admissions for hydrocele management are documented in state hospitals' Indoor Morbidity and Mortality Registers.

This study aimed to examine the impact of the NPELF on LF chronic disease manifestations using Passive Case Detection (PCD) data maintained in filaria clinics and hospital indoor morbidity and mortality registers. The trends in lymphoedema PCD rates were examined (overall and district-wise) by a retrospective analysis of clinic data since initiating the LF elimination program in Sri Lanka to identify and anticipate disease patterns and directions. The hospital inpatient records for hydrocele/spermatocele management from 2007–2022 throughout the country were examined for trends.

# Methods

The Ethics Review Committee of the Faculty of Medicine, University of Kelaniya granted ethics exemption for the study. The study was an audit of data archives and current data (available in the public domain) of the National Anti-Filariasis Campaign.

#### Analysis of current status

The lymphoedema case attendance at filaria clinics in 2022 for the eight endemic districts in three provinces was obtained from the recently established online platform at Anti-Filariasis Campaign and analyzed to assess the current disease status. For 2022, the overall and district-wise lymphoedema PCD rate per 10,000 population was calculated using the estimated respective populations [15].

#### **Retrospective analysis of PCD trends**

A retrospective analysis was conducted using the data maintained in the filaria clinic registries from 2006 onwards. We extracted data on clinic attendees focusing on the first clinic visits (new lymphoedema case visits) to filaria clinics from 2006 to 2022, which served as a proxy for disease incidence. Information regarding the estimated population in the endemic districts for the relevant years was obtained from the national censuses of 2001 and 2012 [15,16]. The age distribution of new lymphoedema cases was analyzed using the available data from 2019 onwards. The district-wise clinic attendance data was available from 2012 onwards, and choropleth maps were used to visualize the district-wise reported lymphoedema PCD rates.

Separate Poisson log-linear models were used to assess the overall and district-wise trends in PCD rates. The number of PCD cases was used as the response variable, and the total respective population of interest was considered a log offset in the models. Time since 2006 was considered as the explanatory variable in the overall model, and time since 2012 was considered the explanatory variable in the district-wise models. Piece-wise and quadratic functions for a time were considered appropriate to model non-linear trends. All the fitted models showed overdispersion, and quasi-Poisson models were adopted.

The annual country-wide data on state hospital admissions for the management of hydrocele/spermatocele from 2007 to 2022 was extracted from the indoor morbidity and mortality registers. The Poisson log-linear model was used to assess the trends in hospital admissions, considering the number of admissions as the response variable and the total male population as a log offset in the models. The time since 2007 was considered as the explanatory variable with a piece-wise function to model non-linear trends. The fitted model showed overdispersion, and the quasi-Poisson model was adopted.

A P value <0.05 was considered as significant. R programming language 4.4.0 was used for analysis.

# Results

#### New lymphoedema case presentations in 2022 in the endemic region

In 2022, 566 patients with lymphoedema received MMDP services for the first time at Filaria clinics (i.e. first clinic visits). The mean age of these patients was 53.9 (SD 16.0) years. Three percent (n = 15) of those seeking care were less than 21 years of age. The demography and disease severity of the new clinic attendees is given in Table 1. Data on lymphoedema severity was documented for 94%, of which 79% were in the early stages (57.3% and 21.4% in stages two and one, respectively). Most (52%,) were from the Western Province (Colombo 108, Gampaha 52, Kalutara 113), while 32% were from Southern (Galle 30, Matara 74, Hambantota 27) and 16% from Northwestern (Kurunegala 98, Puttalam 63) Provinces. In 2022, the reported overall PCD rate for lymphoedema was 0.61 per 10,000 in the endemic population, while the districts of Matara (1.11 per 10,000), Puttalam (0.78 per 10,000) and Kalutara (0.68 per 10,000) reported the highest PCD rates.

Variables	Western Province			Southern Province		North Western Province		Non-endemic	Total	
	Colombo	Gampaha	Kalutara	Galle	Matara	Hambantota	Kurunegala	Puttalam		N (%)
Age group										
<21 years	01	04	01	00	00	00	07	03	00	16 (2.8)
21-30 years	06	00	08	00	02	01	07	04	01	29 (5.1)
31-40 years	08	06	11	02	06	05	12	11	00	61 (10.8)
41-50 years	27	14	26	08	07	09	19	12	00	122 (21.6)
51-60 years	23	09	26	04	13	05	18	13	00	111 (19.6)
61-70 years	29	12	29	10	26	05	18	16	00	145 (25.6)
>70 years	12	07	12	06	16	00	16	04	00	74 (13.1)
Unspecified	02	-	-	-	04	02	-	-	-	08 (1.4)
Sex										
Female	59	23	55	12	40	12	49	36	00	286 (50.5)
Male	48	29	58	18	32	14	49	27	01	276 (48.8)
Unspecified	01	-	-	-	02	01	-	-	-	04 (0.7)
Stage										
Ι	15	11	21	04	29	07	08	18	01	114 (20.1)
II	70	32	64	09	15	14	63	38	00	305 (53.9)
III	15	07	16	05	07	04	24	03	00	81 (14.3)
IV	01	01	03	05	01	00	02	00	00	13 (2.3)
v	00	00	04	02	01	00	00	01	00	08 (1.4)
VI	01	01	00	02	00	00	01	02	00	07 (1.2)
VII	00	00	00	03	01	00	00	00	00	04 (0.7)
Unspecified	06	-	05	-	20	02	-	01	-	34 (6.0)
Total	108	52	113	30	74	27	98	63	01	566 (100)

https://doi.org/10.1371/journal.pntd.0012343.t001

### Retrospective analysis of new lymphoedema cases

The reported overall PCD rate in the endemic districts in 2006 was 2 per 10,000, which had declined to 0.6 per 10,000 in 2022. Fig 1 shows the endemic districts for filariasis and changes in district-wise reported PCD rates of lymphoedema from 2012 to 2022. The observed PCD rates showed different time trends in the seven endemic districts.

The fitted log-linear models for overall PCD rates from 2006 to 2022 and district-wise PCD rates from 2012 to 2022 are shown in Table 2. The overall PCD rate had declined from 2006 to 2022 at a rate of 7.6% (95%CI: 4.9% - 10.3%) per year (P < 0.0001). The estimated overall PCD rate from the fitted model for 2022 was 0.45 (95%CI: 0.33–0.61) per 10,000. The district-wise PCD rates showed declining trends in three of the seven endemic districts: 14.5% (10.3% - 18.7%) per year in Colombo, 6.9% (1.4% - 12.3%) per year in Gampaha and 12.0% (8.3% - 17.3%) per year in Kurunegala. Puttalam and Galle showed quadratic trends; PCD rates rose till 2018 in Puttalam and till 2017 in Galle, and rates went down thereafter. In Matara, PCD rose till 2014, and rates showed a slight downward trend thereafter. The PCD rate remained static in the Kalutara district (Fig 2). The Hambantota district was excluded from the analysis as it did not have MMDP coverage until 2022. The age distribution of new lymphoedema cases throughout the endemic districts from 2019–2022 showed a rising frequency with age, with the average case presenting in the 6<sup>th</sup> decade (Table 3).

### Trends in the inpatient management of hydroceles/spermatoceles

A total of 37,557 patients were admitted for management for hydroceles/spermatoceles in state hospitals from 2007 to 2022. This was 2,717 in 2007 and 1,869 in 2022. The fitted log-linear model



**Fig 1. The district-wise reported PCD rates of lymphoedema after implementing the national programme to eliminate lymphatic filariasis in Sri Lanka.** District-wise reported PCD rates of lymphedema from 2012 to 2022. The grey colour area in the top left map indicates the endemic districts of lymphatic filariasis in Sri Lanka. Subsequent maps show the district-wise PCD rates from 2012 to 2022. The base map shapefile was downloaded from The Humanitarian Data Exchange website (https://data.humdata.org/dataset/cod-ab-lka). The content on this site is licensed under a Creative Commons Attribution 4.0 International license (https://data.humdata.org/dataset).

https://doi.org/10.1371/journal.pntd.0012343.g001

for hospital admission for the management of hydroceles/spermatoceles is shown in Table 4. Hospital admissions remain static from 2007 to 2015 (P = 0.338). Thereafter, hospital admissions declined till 2022 at a rate of 7% per year (95% CI: 4% - 11% per year, P = 0.001) (Fig 3).

## Discussion

The focus of this study was to evaluate the impact of the mass treatment program on the burden of chronic lymphatic morbidity, from a clinical perspective rather than an epidemiological perspective of risk-of-infection (represented by MF rates, and mosquito infection and infective rates). During 2001–2019, the national program delivered a total of 52.8 million treatments of which 44.8 million treatments were consumed by a target population of 10.46 million [17].

Clinically, filarial lymphoedema is indistinguishable from lymphoedema due to other causes and the lack of a specific diagnostic tool to trace the etiology of lymphoedema and hydrocele, to filarial origin would have affected this assessment, the magnitude of which is unknown. The lack of baseline epidemiological data on morbidity and the absence of an active case surveillance program hindered achieving the study objectives to a greater extent. The impact of preventive chemotherapy on lymphatic morbidity was assessed utilizing passive case detection data.

The onset of lymphoedema in filariasis endemic areas generally occurs around puberty, and prevalence rises progressively with age [13]. The age distribution of first clinic-visit attendees reflects the epidemiological pattern of filarial lymphoedema, with case numbers progressively increasing with age (Tables 1 and 3). The disease distribution was similar among both sexes (Table 1). Most cases were in early lymphoedema (stages 2 and 1) according to WHO criteria

	Estimate	Std. Err.	T value	P value
Overall: from 2006 to 2022				
Intercept	-1.7837	0.117	-15.688	< 0.0001
Time (year)	-0.079	0.019	-5.369	< 0.0001
Colombo district: from 2012 to 2022				
Intercept	-1.565	0.1159	-13.50	< 0.0001
Time (year)	-0.157	0.0250	-6.280	0.0001
Gampaha district: from 2012 to 2022				
Intercept	-2.337	0.160	-14.568	< 0.0001
Time (year)	-0.073	0.030	-2.412	0.0391
Kalutara district: from 2012 to 2022	-2.989	0.253	-11.833	
Intercept	5.143	85.920	0.060	0.9540
Time (year)	-0.004	0.043	-0.095	0.9260
Kurunegala district: from 2012 to 2022	-3.499	0.126	-27.846	
Intercept	273.793	52.759	5.190	0.0006
Time (year)	-0.138	0.026	-5.266	0.0005
Puttalam district: from 2012 to 2022				
Intercept	-3.638	0.341	-10.656	< 0.0001
Time (year)	0.587	0.133	4.411	0.0030
Time <sup>2</sup> (year)	-0.049	0.012	-4.194	0.0030
Galle district: from 2012 to 2022				
Intercept	-1.151e+05	4.828e+04	-2.384	0.044
Time (year)	1.141e+02	4.787e+01	2.384	0.044
Time <sup>2</sup> (year)	-2.829e-02	1.187e-02	-2.384	0.044
Matara district: from 2012 to 2022				
Intercept	-5.232	0.671	-7.795	< 0.0001
Time (year)	1.425	0.349	4.071	0.0036
Time > 2014 (year)	-1.435	0.358	-4.003	0.0039

#### Table 2. Parameter estimates of the fitted log-linear models.

https://doi.org/10.1371/journal.pntd.0012343.t002

[18]. The frequency of cases was highest in the districts of Kalutara (118) and Colombo (108) in Western Province. However, the case distribution per population was highest for Matara, and Puttalam districts.

Previous studies have examined the impact of MDA on filarial lymphoedema with variable results, some reporting reductions in chronic manifestations while some observed reductions in acute manifestations [19–25]. Studies conducted prior to the elimination drive utilized different treatment regimens from those utilized in the global program for the elimination of LF. Reductions in MF rates, elephantiasis and hydroceles were reported in Tahiti following five years of standard DEC therapy combined with vector control, in Indonesia 11 years of MDA with DEC reported reductions in elephantiasis, acute attacks and MF rates while in China six months of DEC medicated table salt reduced acute manifestations but chronic manifestations were unchanged or aggravated [19–21]. Similarly, studies conducted after the global elimination drive also report mixed results [22–25]

In the present evaluation, the new lymphoedema case visits presenting for MMDP services nearly sixteen years after five rounds of MDAs show a 70% reduction from 2 per 10,000 populations in 2006 following the fifth round of preventive chemotherapy to 0.6 per 10,000 population in 2022. The average infection parameters, MF and infective mosquito rates have shown a steady decline to its current low value of 0.03% for both indices suggesting that Sri Lanka is nearing transmission breakpoints with eventual cessation of transmission (risk-of-infection



Fig 2. Observed and predicted overall passive case detection rates from 2006 to 2022 and district-wise rates from 2012 to 2022. Observed PCD rates (black dots) and predicted PCD rates (black lie) with 95% Confidence Interval (grey colour band) from the fitted log-linear models.

https://doi.org/10.1371/journal.pntd.0012343.g002

nearing zero) [8]. The overall declining trends in new lymphoedema case detection rates provide supportive evidence. However, district-wise data indicate that the declining trend is not uniform throughout the endemic region. Declining trends in PCD rates were observed in three districts, Colombo, Gampaha and Kurunegala. The district of Kurunegala was a low transmission region in the pre-elimination era and five rounds of MDAs would have sufficed in interrupting transmission. The district of Colombo (where the capital city is located) and the adjacent district Gampaha, probably experienced more socioeconomic and infrastructure development than the other regions thus lowering vector densities and transmission. In the other four districts a steady decline was not evident. Thus, a careful epidemiological assessment of these four districts may be a worthwhile effort.

The disease dynamics of LF is an important aspect that needs to be considered as the appearance of chronic manifestations such as lymphoedema occurs about a decade after the infection. Thus, the disease rates reflect the infection dynamics a decade ago. Therefore, historical surveillance data prior to validation was important. The southern districts of Matara and Galle were high LF endemic districts in the pre-elimination era with an average MF prevalence of 4.4% and MF density of 20 /60µl of blood [26]. Even after cessation of the MDA (nine years post-MDA), there was strong evidence of persistent transmission, with vector infection rates by molecular xenomonitoring (filarial DNA in *C. quinquefasciatus*, principal vector of *W. bancrofti* in Sri Lanka) above the threshold value of 1% [27].

The emergence of brugian filariasis infections of zoonotic origin with the district of Puttalam being the epicenter of the outbreak was reported about a decade ago [28,29]. The entomological surveillance data in the district of Puttalam support ongoing transmission [10]. As of now, the emerging brugian filariasis infection has spread to other endemic districts particularly Kalutara, and Galle. Therefore, it may be presumed that evaluation may be premature in the districts of Puttalam and Kalutara (reemerged brugia infections), Matara and Galle (former high transmission regions) to observe a steady declining trend in lymphatic morbidity rates.

Thus the variable decline in PCD rates of lymphoedema observed across the endemic region may be due to the heterogeneity in transmission. Factors such as low baseline MF

Colombo         Image (years)         562         52.7         52.2         55.4           0-20 years         9         3         6         0.0         11           41-60 years         99         61         29         54           61-80 years         99         61         29         54           61-80 years         99         61         29         37           81-100 years         5         5         3         11           Gampaha	Age category by district	2019	2020	2021	2022
Mean Age (years)56252.752.255.4 $0^{-2}$ (years)93600 $21-40$ years27247111 $41-60$ years99612954 $61-80$ years113382037 $81-100$ years55311 <b>Campaha</b> $$	Colombo				
0-20 years         9         3         6         0           21-40 years         27         24         7         11           41-60 years         99         61         29         54           61-80 years         113         38         20         37           81-100 years         5         5         3         1           Gampaha	Mean Age (years)	56.2	52.7	52.2	55.4
21-40 years $27$ $24$ $7$ $11$ $41-60$ years         99 $61$ 29 $54$ $61-80$ years         5         5         3 $17$ <b>Gampaha</b>	0–20 years	9	3	6	0
41-60 years         99         61         29         54           61-80 years         113         3.8         20         37           Sh-100 years         5         5         3         11           Gampaha               Mean Age (years)         57.6         51.1         49.8         53.1           0-20 years         2         3         2         11           21-40 years         19         31         23         19           41-60 years         64         37         30         31           61-80 years         86         39         26         30           81-100 years         1         2         0         2           Katara            0         0           21-40 years         9         3         3         11         1         0         0           21-40 years         49         8         8         44         44         81-100 years         1         1         0         2           Gale             1         1         1         1         1	21-40 years	27	24	7	11
61-80 years         113         38         20         37           81-100 years         5         5         3         1           Gampah         2         3         2         11           0-20 years         2         3         2         11           21-40 years         19         31         23         19           41-60 years         64         37         30         31           61-80 years         86         39         26         30           81-100 years         1         2         0         2           Kalutar	41-60 years	99	61	29	54
81-100 years         5         5         3         1           Gampaha	61-80 years	113	38	20	37
Gampaha         Image (years) $57.6$ $51.1$ $49.8$ $53.1$ $0-20$ years         2         3         2         1 $21-40$ years         19         31         23         19 $41-60$ years         64         37         30         31 $61-80$ years         86         39         26         30 $81-100$ years         1         2         0         2           Mean Age (years)         56.4         52.6         54.5         58.4 $0-20$ years         4         1         0         0         0 $21-40$ years         44         25         11         31         1 $41-60$ years         44         25         11         31         1         0         0         2 $41-60$ years         44         25         11         31         1         0         2 $6ale$ 2         1         3         5 $6ale$ 2         50         55.2         51.6 $0-20$ years <td< td=""><td>81-100 years</td><td>5</td><td>5</td><td>3</td><td>1</td></td<>	81-100 years	5	5	3	1
Mean Age (years) $57.6$ $51.1$ $49.8$ $53.1$ $0-20$ years19312319 $21-40$ years64373031 $61-80$ years86392630 $81-100$ years1202Kaltara </td <td>Gampaha</td> <td></td> <td></td> <td></td> <td></td>	Gampaha				
0-20 years2321 $21-40$ years19312319 $41-60$ years64373031 $61-80$ years86392630 $81-100$ years1202Kalutara	Mean Age (years)	57.6	51.1	49.8	53.1
21-40 years19312319 $41-60$ years $64$ $37$ $30$ $31$ $61-80$ years1 $2$ $0$ $2$ $81-100$ years1 $2$ $0$ $2$ Kalutara $0$ $0$ $2$ Kalutara $0$ $0$ Mean Age (years) $56.4$ $52.6$ $54.5$ $58.4$ $0-20$ years $4$ $1$ $0$ $0$ $21-40$ years $44$ $25$ $11$ $31$ $61-80$ years $44$ $25$ $11$ $31$ $61-80$ years $44$ $25$ $11$ $31$ $61-80$ years $49$ $8$ $8$ $44$ $81-100$ years $1$ $1$ $0$ $2$ $Gale$ $-20$ $2$ $20$ $7$ $Mean Age (years)$ $52.2$ $50.7$ $53.2$ $51.6$ $0-20$ years $9$ $4$ $2$ $44$ $2$ $21-40$ years $16$ $18$ $3$ $55$ $41-60$ years $2$ $20$ $0$ $0$ Matara $-20$ $0$ $0$ $1$ $Mean Age (years)$ $57.9$ $60.7$ $50.7$ $50.8$ $<20$ years $2$ $10$ $3$ $7$ $21-40$ years $29$ $21$ $27$ $37$ $61-80$ years $29$ $21$ $27$ $37$ $61-80$ years $38$ $21$ $15$ $34$ $41-00$ years $1$ $0$	0–20 years	2	3	2	1
41-60 years64373031 $61$ -80 years86392630 $81$ -100 years1202Kalutara </td <td>21-40 years</td> <td>19</td> <td>31</td> <td>23</td> <td>19</td>	21-40 years	19	31	23	19
61-80 years         86         39         26         30           81-100 years         1         2         0         2           Mean Age (years)         56.4         52.6         54.5         58.4           0-20 years         4         1         0         0         0           21-40 years         9         3         3         111         31           41-60 years         44         25         11         31         61-80 years         44         25         11         31           61-80 years         49         8         8         44         <	41-60 years	64	37	30	31
81-100 years         1         2         0         2           Kahutara	61-80 years	86	39	26	30
KalutaraImage: constraint of the system of the	81-100 years	1	2	0	2
Mean Age (years)         56.4         52.6         54.5         58.4           0-20 years         4         1         0         0           21-40 years         9         3         3         11           41-60 years         44         25         11         31           61-80 years         49         8         8         44           81-100 years         1         1         0         2           Gale	Kalutara				
0-20 years         4         1         0         0           21-40 years         9         3         3         11           41-60 years         44         25         11         31           61-80 years         49         8         8         44           81-100 years         1         1         0         2           Galle	Mean Age (years)	56.4	52.6	54.5	58.4
21-40 years         9         3         3         11           41-60 years         44         25         11         31           61-80 years         49         8         8         44           81-100 years         1         1         0         2           Gale	0–20 years	4	1	0	0
41-60 years         44         25         11         31           61-80 years         49         8         8         44           81-100 years         1         1         0         2           Gale	21-40 years	9	3	3	11
61-80 years         49         8         8         44           81-100 years         1         1         0         2           Gale	41-60 years	44	25	11	31
81-100 years         1         1         0         2           Galle	61-80 years	49	8	8	44
Galle         Mean Age (years)         52.2         50.7         53.2         51.6           0-20 years         9         4         2         4           21-40 years         16         18         3         5           41-60 years         40         35         9         24           61-80 years         42         25         11         17           81-100 years         2         2         0         0           Matara	81-100 years	1	1	0	2
Mean Age (years)52.250.753.251.6 $0-20$ years9424 $21-40$ years161835 $41-60$ years4035924 $61-80$ years42251117 $81-100$ years2200MataraMean Age (years)57.960.750.7 $50.8$ 21037 $21-40$ years624918 $41-60$ years29212737 $61-80$ years38211534 $81-100$ years1011Kurnegala </td <td>Galle</td> <td></td> <td></td> <td></td> <td></td>	Galle				
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Mean Age (years)	52.2	50.7	53.2	51.6
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	0–20 years	9	4	2	4
41-60 years         40         35         9         24           61-80 years         42         25         11         17           81-100 years         2         2         0         0           Mean Age (years)         57.9         60.7         50.7         50.8           <20 years	21-40 years	16	18	3	5
61-80 years         42         25         11         17           81-100 years         2         2         0         0           Mean Age (years)         57.9         60.7         50.7         50.8           <20 years	41-60 years	40	35	9	24
81-100 years         2         2         0         0           Matara	61-80 years	42	25	11	17
Matara         Mean Age (years)         57.9         60.7         50.7         50.8            <20 years	81-100 years	2	2	0	0
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Matara				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean Age (years)	57.9	60.7	50.7	50.8
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	<20 years	2	10	3	7
41-60 years2921273761-80 years3821153481-100 years1011KurunegalaMean Age (years)60.035.332.760.820 years04421-40 years235241-60 years7861061-80 years10001281-100 years1002Puttalam22020 years10104321-40 years54.250.745.149.2<20 years	21-40 years	6	24	9	18
61-80 years         38         21         15         34           81-100 years         1         0         1         1           Kurunegala               Mean Age (years)         60.0         35.3         32.7         60.8           <20 years	41-60 years	29	21	27	37
81-100 years         1         0         1         1           Kurunegala         60.0         35.3         32.7         60.8           <20 years         0         4         4         0           21-40 years         2         3         5         2           41-60 years         7         8         6         10           61-80 years         10         0         0         12           81-100 years         1         0         0         2           Puttalam         2         50.7         45.1         49.2           <20 years         10         10         4         3           21-40 years         54.2         50.7         45.1         49.2            54.2         50.7         45.1         49.2            10         10         4         3            10         10         4         3            16         14         20         16            62         29         24         39	61-80 years	38	21	15	34
KurunegalaImage (years)60.035.332.760.8<20 years	81-100 years	1	0	1	1
$\begin{tabular}{ c c c c c c c } \hline Mean Age (years) & 60.0 & 35.3 & 32.7 & 60.8 \\ \hline <20 years & 0 & 4 & 4 & 0 \\ \hline 21-40 years & 2 & 3 & 5 & 2 \\ \hline 41-60 years & 7 & 8 & 6 & 10 \\ \hline 61-80 years & 10 & 0 & 0 & 12 \\ \hline 81-100 years & 10 & 0 & 0 & 2 \\ \hline Puttalam & & & & \\ \hline Mean Age (years) & 54.2 & 50.7 & 45.1 & 49.2 \\ \hline <20 years & 10 & 10 & 4 & 3 \\ \hline 21-40 years & 16 & 14 & 20 & 16 \\ \hline 41-60 years & 62 & 29 & 24 & 39 \\ \hline \end{tabular}$	Kurunegala				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean Age (years)	60.0	35.3	32.7	60.8
21-40 years         2         3         5         2           41-60 years         7         8         6         10           61-80 years         10         0         0         12           81-100 years         1         0         0         2           Puttalam	<20 years	0	4	4	0
41-60 years         7         8         6         10           61-80 years         10         0         0         12           81-100 years         1         0         0         2           Puttalam	21-40 years	2	3	5	2
61-80 years         10         0         0         12           81-100 years         1         0         0         2           Puttalam               49.2           Mean Age (years)         54.2         50.7         45.1         49.2          3          21-40 years         10         10         4         3           16         14         20         16          41-60 years         62         29         24         39          39           39           39           39           39           39           39            39            39	41-60 years	7	8	6	10
81-100 years         1         0         0         2           Puttalam	61-80 years	10	0	0	12
Puttalam         Mean Age (years)         54.2         50.7         45.1         49.2           <20 years	81-100 years	1	0	0	2
Mean Age (years)         54.2         50.7         45.1         49.2           <20 years	Puttalam				
<20 years         10         10         4         3           21-40 years         16         14         20         16           41-60 years         62         29         24         39	Mean Age (years)	54.2	50.7	45.1	49.2
21-40 years         16         14         20         16           41-60 years         62         29         24         39	<20 years	10	10	4	3
41-60 years         62         29         24         39	21-40 years	16	14	20	16
	41-60 years	62	29	24	39

Table 3. Age distribution of new lymphoedema patient visits to filaria clinics by districts (2019-2022).

(Continued)

Table 3. (	(Continued)
------------	-------------

Age category by district	2019	2020	2021	2022
61-80 years	64	35	13	17
81–100 years	2	1	0	1
Sri Lanka				
Mean Age (years)	55.9	50.0	49.2	53.6
<20 years	36	35	21	15
21-40 years	95	117	70	87
41-60 years	345	216	136	244
61–80 years	402	166	91	198
81–100 years	13	11	4	9

https://doi.org/10.1371/journal.pntd.0012343.t003

prevalence prior to MDA (district of Kurunegala) and socioeconomic growth leading to declines in vector densities (district of Colombo and Gampaha) would have contributed to the steady decline in morbidity while persistence of bancroftian filariasis in small pockets of high baseline prevalence regions (districts of Matara and Galle), emergence of zoonotic brugian filariasis (Kalutara and Puttalam) are challenges to declines in morbidity rates while non-infection parameters such as an improved referral rates to filarial clinics may also have contributed to maintenance or rising trends in morbidity.

The explanations for new lymphoedema case detections after elimination of LF as a public health problem may vary according to region. Some cases may represent late manifestations of asymptomatic infections, some may represent early manifestations of newly acquired infections of bancroftian (southern districts of Matara and Galle) or brugian filariasis (districts of Puttalam and Kalutara) while some lymphoedema cases may be of non-filarial origin (primary lymphoedema or other secondary cause). The latter two may explain the occurrence of new cases among the younger population (<20 years).

Unlike the lymphatic pathology, the presence of adult worms alone is sufficient to cause hydroceles [30]. Thus, the reduction of adult worm burden with repeated MDAs with antifilarial drugs which have a partial adulticidal effect should reduce the hydrocele prevalence. However, the hospital admission rates for hydrocele management remained static until 2015 (nearly a decade following conclusion of MDA) and only thereafter a declining trend was evident. (Fig 3). The delayed decline observed may have been caused by the backlog clearance of hydrocele/ spermatocele surgeries. A review of the literature reports that four rounds of MDA with either DEC/ivermectin achieved a maximum of 60% reduction in hydrocele prevalence and beyond that there was no additional impact [31].

This report provides a glimpse of the lymphatic filariasis morbidity trends, two decades following the NPELF consisting of five rounds of MDAs with DEC and albendazole in an area endemic to bancroftian filariasis and a re-emerging zoonotic *B. malayi*. It is timely to ascertain the national case burden of lymphoedema and hydrocele by active surveillance and to monitor

Table 4.	Parameter estimates of the fitted lo	g-linear model for hos	pital admission rate for the mana	gement of hydroceles/spermatoceles.

	Estimate	Std. Err.	T value	P value
Overall				
Intercept	16.517886	17.949465	0.920	0.37421
Time (year)	-0.008876	0.008924	-0.995	0.33805
Time > 2015 (year)	-0.075336	0.018445	-4.084	0.0012

Observed hospital admission rates (black dots) and predicted rates (black lie) with 95% Confidence Interval (grey colour band) from the fitted log-linear models.

https://doi.org/10.1371/journal.pntd.0012343.t004



Fig 3. Hospital admission rates for management of hydrocele/spermatocele in Sri Lanka following the mass drug administration program (2007–2022).

https://doi.org/10.1371/journal.pntd.0012343.g003

the trends in disease rates, particularly in the districts showing static trends or marginal nonsignificant declines in PCD rates. The factors discussed herein may be contributing factors for the variable declining trends in chronic filariasis morbidity observed in the country. Other factors such as hygiene-related factors (environmental and personal) and genetic predisposition need consideration and rectification where possible.

Factors such as lack of confidence or excessive enthusiasm in the newly established MMDP services may have affected clinic attendance at the onset or later which may affect the PCD rates and trend lines. The absence of baseline data was a major limitation in the assessment.

### Conclusions

The chronic lymphatic disease rates in the LF endemic region in Sri Lanka, ascertained by PCD, showed a steady decline in the overall endemic region, and, specifically in Colombo, Gampaha and Kurunegala districts. Except for the district of Kalutara, where the lymphoedema PCD rate remained static, all other districts showed declining trends in PCD rates in recent years. Hydrocele/ spermatocele case admission rates to state hospitals showed a downward trend from 2015 onwards, about a decade following the conclusion of MDA. Ascertaining the actual lymphoedema case burden in the country (endemic and non-endemic regions) and monitoring disease trends is required at this juncture of the near elimination of transmission of LF in Sri Lanka. Integration of morbidity management services to the general health system and enhancing services with the inclusion of tertiary care (rehabilitation, psychological and social support), where indicated, is suggested with the reductions in the public health burden of lymphatic filariasis.

### Supporting information

S1 Data. New lymphoedema case numbers registered in filarial clinics district wise from 2012–2022 with the estimated population for the relevant years. (CSV)

S2 Data. Patient numbers admitted to state hospitals in Sri Lanka for management of hydrocele/spermatocoeles from 2007–2022 with the estimated mid-year male population. (CSV)

#### Acknowledgments

The authors gratefully acknowledge the dedication of the Filaria clinic staff towards data maintenance while providing morbidity prevention and alleviation services to patients with lymphoedema and the Directors of the Anti-Filariasis Campaign, for their leadership, guidance and dedication for lymphatic filariasis elimination. We also acknowledge the support extended by the Medical Statistics Division of the Ministry of Health.

#### **Author Contributions**

**Conceptualization:** Indeewarie E Gunaratna, Nilmini T. G. A Chandrasena, Ranjan Premaratna.

Data curation: Indeewarie E Gunaratna, Murali Vallipuranathan.

Formal analysis: Indeewarie E Gunaratna, Nilmini T. G. A Chandrasena, Dileepa Ediriweera.

**Investigation:** Indeewarie E Gunaratna, Nilmini T. G. A Chandrasena, Murali Vallipuranathan.

Methodology: Nilmini T. G. A Chandrasena.

Supervision: Nilanthi R de Silva.

Writing - original draft: Nilmini T. G. A Chandrasena, Ranjan Premaratna.

Writing – review & editing: Dileepa Ediriweera, Nilanthi R de Silva.

#### References

- WHO. Bridging the Gap, The World Health Report, World Health Organization. 1995; Geneva, Switzerland.
- Ottesen EA. The global programme to eliminate lymphatic filariasis. Trop Med Int Health. 2000 Sep; 5 (9):591–4. https://doi.org/10.1046/j.1365-3156.2000.00620.x PMID: 11044272.
- Taylor M.J., Hoerauf A. and Bockarie M. Lymphatic Filariasis and Onchocerciasis. The Lancet. 2010; 376: 1175–1185. https://doi.org/10.1016/S0140-6736(10)60586-7 PMID: 20739055
- Simonsen P, Fischer P, Hoerauf A, Weil G. The Filariases In Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White NJ. editors Manson's Tropical Diseases 23. Philadelphia: Elsevier Saunders; 2014. P 737–765,
- 5. WHO. Lymphatic Filariasis. (WHO Fact Sheet 190) World Health Organization 1998; Geneva, Switzerland.
- WHO. Preparing and implementing a national plan to eliminate lymphatic filariasis (in countries where onchocerciasis is not co-endemic) World Health Organization 2000; Geneva, Switzerland. WHO/CDS/ CPP/CEE 200016.
- WHO. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization 2020; Geneva, Switzerland. (https://www.who.int/publications/i/item/9789240010352).
- Chandrasena NTGA Gunaratna IE, Ediriweera D, de Silva NR. Lymphatic filariases and soil-transmitted helminthiases in Sri Lanka: the challenge of eliminating residual pockets of transmission. Philos Trans R Soc Lond B Biol Sci. 2023 Oct 9; 378(1887):20220280. https://doi.org/10.1098/rstb.2022.0280 Epub 2023 Aug 21. PMID: 37598710; PMCID: PMC10440162.
- 9. World Health Organization 2016 Maldives and Sri Lanka eliminate lymphatic filariasis. Available from: http://wwwsearo.who.int/mediacentre/releases/2016/1626/en/

- 10. AFC. Annual Statistical Bulletin 2019–2022. Anti-Filariasis Campaign, Ministry of Health Nutrition and Indigenous Medicine Sri Lanka.
- Perera M, Whitehead M, Molyneux D, Weerasooriya M, Gunatilleke G. Neglected patients with a neglected disease? A qualitative study of lymphatic filariasis. PLoS Negl Trop Dis. 2007 Nov 21; 1(2): e128. https://doi.org/10.1371/journal.pntd.0000128 PMID: 18060080; PMCID: PMC2100378.
- Yahathugoda TC, Wickramasinghe D, Weerasooriya MV, Samarawickrema WA. Lymphoedema and its management in cases of lymphatic filariasis: the current situation in three suburbs of Matara, Sri Lanka, before the introduction of a morbidity-control programme. Ann Trop Med Parasitol. 2005 Jul; 99 (5):501–10. https://doi.org/10.1179/136485905X46450 PMID: 16004709.
- Addiss DG, Brady MA. Morbidity management in the Global Programme to Eliminate Lymphatic Filariasis: a review of the scientific literature. Filaria J. 2007 Feb 15; 6:2. https://doi.org/10.1186/1475-2883-6-2 PMID: 17302976; PMCID: PMC1828725.
- Chandrasena N, Premaratna R, Gunaratna IE, de Silva NR. Morbidity management and disability prevention for lymphatic filariasis in Sri Lanka: Current status and future prospects. PLoS Negl Trop Dis. 2018 May 10; 12(5):e0006472. https://doi.org/10.1371/journal.pntd.0006472 PMID: 29746479; PMCID: PMC5963805.
- Department of Census and Statistics. Census of Population and Housing 2012. Department of Census and Statistics, Sri Lanka. <u>http://www.statistics.gov.lk/Population/StaticalInformation/CPH2011</u>. Accessed 11th December 2023.
- 16. Department of Census and Statistics Archives. Census of Population and Housing 2001. Department of Census and Statistics, Sri Lanka.
- Kapa DR, Mohamed AJ. Progress and impact of 20 years of a lymphatic filariasis elimination programme in South-East Asia. Int Health. 2020 Dec 22; 13(Suppl 1):S17–S21. https://doi.org/10.1093/ inthealth/ihaa056 PMID: 33349881; PMCID: PMC7753165.
- WHO. Lymphoedema staff manual: Treatment and Prevention of Problems associated with Lymphatic filariasis- Part -1. Learners Guide. World Health Organization; Geneva, Switzerland. WHO/CDS/CDE/ CEE/2001.26a.
- March HN, Laigret J, Kessel JF, Bambridge B. Reduction in the prevalence of clinical filariasis in Tahiti following adoption of a control program. Am J Trop Med Hyg. 1960 Mar; 9:180–4. <u>https://doi.org/10. 4269/ajtmh.1960.9.180 PMID: 14420863.</u>
- Partono F, Maizels RM, Purnomo. Towards a filariasis-free community: evaluation of filariasis control over an eleven year period in Flores, Indonesia. Trans R Soc Trop Med Hyg. 1989 Nov-Dec; 83(6):821– 6. https://doi.org/10.1016/0035-9203(89)90343-x PMID: 2617653.
- Fan PC, Peng HW, Chen CC. Follow-up investigations on clinical manifestations after filariasis eradication by diethylcarbamazine medicated common salt on Kinmen (Quemoy) Islands, Republic of China. J Trop Med Hyg. 1995 Dec; 98(6):461–4. PMID: 8544232.
- 22. Yuvaraj J, Pani SP, Vanamail P, Ramaiah KD, Das PK. Impact of seven rounds of mass administration of diethylcarbamazine and ivermectin on prevalence of chronic lymphatic filariasis in south India. Trop Med Int Health. 2008 May; 13(5):737–42. https://doi.org/10.1111/j.1365-3156.2008.02044.x Epub 2008 Mar 12. PMID: 18346027.
- 23. Shenoy RK, Suma TK, Kumaraswami V, Rahmah N, Dhananjayan G, Padma S. Antifilarial drugs, in the doses employed in mass drug administrations by the Global Programme to Eliminate Lymphatic Filariasis, reverse lymphatic pathology in children with Brugia malayi infection. Ann Trop Med Parasitol. 2009 Apr; 103(3):235–47. https://doi.org/10.1179/136485909X398249 PMID: 19341538.
- Bockarie MJ, Tisch DJ, Kastens W, Alexander ND, Dimber Z, Bockarie F. et al. Mass treatment to eliminate filariasis in Papua New Guinea. N Engl J Med. 2002 Dec 5; 347(23):1841–8. https://doi.org/10. 1056/NEJMoa021309 PMID: 12466508.
- 25. Dickson BFR, Graves PM, Aye NN, Nwe TW, Wai T, Win SS. et al. The prevalence of lymphatic filariasis infection and disease following six rounds of mass drug administration in Mandalay Region, Myanmar. PLoS Negl Trop Dis. 2018 Nov 12; 12(11):e0006944. https://doi.org/10.1371/journal.pntd. 0006944 PMID: 30419025; PMCID: PMC6258426.
- Weerasooriya MV, Weerasooriya TR, Gunawardena NK, Samarawickrema WA, Kimura E. Epidemiology of bancroftian filariasis in three suburban areas of Matara, Sri Lanka. Ann Trop Med Parasitol. 2001 Apr; 95(3):263–73. https://doi.org/10.1080/00034980120051287 PMID: 11339886.
- Rao RU, Nagodavithana KC, Samarasekara SD, Dassanayaka TDM, Punchihewa MW, Ranasinghe USB, Weil GJ. Reassessment of areas with persistent lymphatic filariasis nine years after cessation of mass drug administration in Sri Lanka. PLoS Negl Trop Dis. 2017; 11, e0006066. <u>https://doi.org/10. 1371/journal.pntd.0006066 PMID: 29084213</u>
- 28. Chandrasena NT, Premaratna R, Samarasekera DS, de Silva NR. Surveillance for transmission of lymphatic filariasis in Colombo and Gampaha districts of Sri Lanka following mass drug administration.

Trans R Soc Trop Med Hyg. 2016 Dec; 110(10):620–622. https://doi.org/10.1093/trstmh/trw067 Epub 2016 Nov 5. PMID: 27816936.

- 29. Mallawarachchi CH, Chandrasena TGAN, Premaratna R, Mallawarachchi SMNSM, de Silva NR. Human infection with sub-periodic Brugia Spp. in Gampaha District, Sri Lanka; a threat to filariasis elimination status? Parasit Vectors 2018; 11, 68. https://doi.org/10.1186/s13071-018-2649-3 PMID: 29378620
- Dreyer G, Norões J, Figueredo-Silva J, Piessens WF. Pathogenesis of lymphatic disease in bancroftian filariasis: a clinical perspective. Parasitol Today. 2000 Dec; 16(12):544–8. https://doi.org/10.1016/ s0169-4758(00)01778-6 PMID: 11121854.
- **31.** Ramaiah KD, Ottesen EA. Progress and impact of 13 years of the global programme to eliminate lymphatic filariasis on reducing the burden of filarial disease. PLoS Negl Trop Dis. 2014 Nov 20; 8(11): e3319. https://doi.org/10.1371/journal.pntd.0003319 PMID: 25412180; PMCID: PMC4239120