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Antigen-positive children as possible microfoci of transmission of lymphatic filariasis in low-prevalence areas of Haiti

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2008

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An abstract of
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Abstract

Antigen-positive children as possible microfoci of transmission of lymphatic filariasis in low-prevalence areas of Haiti

By Naomi A. Drexler

Lymphatic filariasis (LF) is a filarial infection associated with severe morbidity that is endemic in over 80 countries, including Haiti. Yet, LF is one of a handful of infectious diseases said to be nearing global elimination. Many populations endemic for LF have seen decreased prevalence over the last decade as availability and use of mass drug treatment has increased. In progression towards global elimination, the World Health Organization recommends that any area with prevalence greater than or equal to 1% should receive mass drug administration (MDA) for at least five consecutive rounds in order to interrupt transmission. It is believed, though not proven, that areas of low-prevalence pose little risk for continued transmission of LF. Five low-prevalence communes identified in the original nation-wide mapping of Haiti in 2001 were utilized in this study: Grand Goâve, Hinche, Moron, St. Louis de Sud and Thomazeau. An initial evaluation of schoolchildren was performed in each commune to help identify antigen-positive children, who could be indicators of transmission within their communities and act as focal points for the subsequent community survey. Two case definitions were employed to identify these sources: index cases (antigen-positive) and antigen-positive ELISA-based autochthonous (AEA) cases (confirmed infections known to be locally acquired). Global Positioning System coordinates and immunochromatographic tests were collected on approximately 1,600 persons of all ages in the five communes. The likelihood of antigen-positive cases being in proximity to index and AEA cases was evaluated using multivariate regression techniques and Bernoulli cluster analyses. Community surveys revealed higher antigen prevalence in three of the five communes than was observed in the original mapping effort. Regression techniques identified a statistically significant increased likelihood of being antigen-positive when living within 20 meters of either index or AEA cases when controlling for age, gender, and commune and spatial clustering of antigen-positive cases was observed in some, but not all communes. Such results indicate that localized transmission was occurring, even in low-prevalence settings. These results suggest that more robust surveillance may be needed in order to detect and extinguish lingering sources of transmission.

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Thank you to you all. I would not be where I am today without you!!

List of Abbreviations:

AEA-Antigen-positive ELISA-based autochthonous
Ag-Antigen
CDC-Centers for Disease Control and Prevention
CFA-Circulating filarial antigen
DEC-Diethylcabamazine
DNA-Deoxyribonucleic acid
ELISA-Enzyme-linked immunosorbant assay
GIS-Geographic information system
GPELF-Global Programme for the Elimination of Lymphatic Filariasis
GPS-Global positioning system
ICT-Immunochromatographic
IRB-Internal review board
LAC-Latin American and the Caribbean
LF-Lymphatic filariasis
LQAS-Lot quality assurance sampling
MDA- Mass drug administration
Mf-Microfilaria
NTD-Neglected tropical disease
PCR-polymerase chain reaction
RAGFIL-Rapid assessment of geographical distribution of Bancroftian filariasis
WHO-World Health Organization

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Chapter 1: Background and Literature Review

Neglected tropical diseases (NTDs) consist of a discrete group of 13 debilitating maladies that are known to chronically infect some of the worlds' poorest individuals (1). Lymphatic filariasis (LF) is one such disease that has begun to receive attention in recent years as initiatives to combat NTDs have gained momentum in the public and private sectors. While LF has been shown to be endemic in over 80 countries worldwide, it is one of only six diseases in 1993 which were deemed to be eradicable (2). Persons suffering from LF can remain asymptomatic for years before presenting with symptoms, by which point irreversible damage has already occurred and can lead to permanent disability. It is estimated that LF is responsible for the loss of 4.6 million disability adjusted life-years (DALYs) worldwide (3).

There are three species of nematodes known to cause lymphatic filariasis: *Wuchereria bancrofti, Brugia malayi and Brugia timori*. LF is most prevalent in sub-Saharan Africa and Central America/Caribbean, where *W bancrofti* is found and in Southeast Asia, where *B malayi* and *B timori* are prevalent. Lymphatic filariasis is caused by a mosquito transmitted thread-like filarial nematode which causes severe lymphedema (swelling) in the lower extremities, and genital areas as lymph tissue is damaged. While LF is not fatal it is extremely debilitating, disfiguring and holds a terrible stigma for those affected. Symptoms can be managed and progression halted, but no cure is known because the damage to the lymph tissue is irreversible and often first present years after the filarial infection.

LF is mosquito transmitted via several species including *Culex, Anopheles, Aedes,* and *Mansonia* and thus, there is a risk of transmission in tropical climates where mosquito populations thrive. LF has a complicated life cycle interacting with its vector as well as the human host and its immune system (see appendix I, Figure 1). Larval filariae develop from microfilariae (mf) in the body of the mosquito and migrate to the mouth parts. Upon biting, the mosquito deposits the immature larvae (L3) onto the skin, the larvae enter the body via the bite wound and migrate to the lymphatic system where the larvae mature into adult worms. Once adult male and female worms mate the female worms release microfilariae back into the blood where they are picked up by another mosquito allowing for the transmission cycle to begin again. The adult worms can persist for years without causing symptoms. Only roughly 10-20% of exposed persons have clinically overt manifestations of disease like lymphedema (4). Adult worms promote lymphatic dysfunction, interfering with the proper exchange of fluids throughout the body causing the classic swelling that is a well known result of LF.

There are several ways to diagnose LF, including a few methods currently in the development phase. The gold standard for diagnosis uses blood samples, typically obtained via finger prick to identify the microfilaria present in the peripheral blood. The microfilaria have a nocturnal cycle in most countries in which they emerge from deep capillary beds and into the blood stream at night, so samples must be obtained at that time and examined utilizing microscopy. A newer approach is based on antigen detection. The immunochromatography

(ICT) cards used for these tests typically only take 10 minutes to read, but results are time-sensitive, and highly subjective. Antigen testing is typically 99% sensitive in persons with detectable microfilaremia. The antigen test can only be used to identifying those who are currently infected with adult worms. The main benefit of using ICT cards for diagnosis is the ease at which these tests can be applied in the field. Antigenemia also can be quantified using enzyme-linked immunosorbant assay (ELISA) techniques in a laboratory setting as antigen can be found in the blood during the daytime, even where microfilariae are nocturnally periodic. Deoxyriboneucleic acid (DNA) based polymerase chain reaction (PCR) tests are available for testing and are highly sensitive but also have little practical application in the field because of the cost and the need for good laboratory infrastructure. Once the filaria develop into adult worms and inhabit the lymph tissue ultrasonography may be used to visualize the movement of the worms in scrotal or lymph tissues; however, this technique has little value for routine diagnosis. The immune system produces antibodies to protect the body against infections. These antibodies are specific to the present infection; they appear early and are maintained after the threat has been eliminated in order to eliminate any re-infection quickly. Currently, antibody diagnostic tests are based on the detection of IgG antibodies to filarial antigens. Antibody testing may provide several advantages, such as detection in urine as well as blood and sera. However, current studies show cross reactivity with other filarial infections (5) limiting the utility of antibody testing where more than one filarial species is present. Scientists

have been working to identify antibody indicators that are specific to *W. bancrofti* to provide a more accurate test.

Several trials have investigated the differences in prevalence estimates amongst the different deterministic tests available including ICT, Og4C3 antigen ELISA, Mf identification via microscopy, BM14 antibody and filarial DNA (6) to compare assay performance. Microfilaremia assessments showed they had the lowest reports overall 4.6% in a study in Leogane, Haiti in 2008, which is consistent with the fact that Mf diagnostics often miss low Mf counts and are unable to detect infections where only adult worms are present and samples can only be collected at night when the microfilaria are circulating. This leads to underestimates of infection prevalence. On the other extreme was the use of BM14 antibody tests, which yielded the highest overall prevalence of 47.0% in the same population (6). Antibody tests, while highly sensitive, may also develop following exposure without the subject actually being infected. Tests of antigenemia, including ICT and Og4C3 are generally thought to be easiest and most consistent measure of prevalence and will be used as the major measure of effect in this study.

Since LF was made a priority by the World Health Organization (WHO) in 1997 there has been much progress in the control and elimination of LF across the globe. In 2000, the WHO developed the Global Programme for the Elimination of Lymphatic Filariasis (GPELF) and set a goal to eliminate LF by 2020. The definition of elimination used by the WHO includes Mf prevalence <1% and evidence that

there is no new parasitic infection in the community (observed, for example, by 5-year cumulative incidence in children born after the start of Mass Drug Administration (MDA) less than 1 per 1,000 children). A "two-pillar" approach has been implemented for the control and elimination of LF which focuses on the interruption of transmission through MDAs and limiting the disability caused by infection by introducing morbidity management programs. MDAs use antifilarial drugs such as diethylcarbamazine (DEC) and ivermectin to kill circulating microfilaria, thus preventing live filaria from being taken up by mosquitoes and continuing transmission. Some programs include the use of vector control to eliminate the mosquitoes known to transmit LF.

As part of the 2004-2009 WHO Regional Strategic Plan for the Elimination of Lymphatic Filariasis mapping of the distribution of LF was considered a priority as it indicates areas where MDAs were necessary and allow for the tracking of progress towards elimination. As of 2009, 68 of the 81 endemic countries had completed mapping of LF (7). Rapid mapping has been a key step in development of elimination programs and several methods have been utilized in the past categorizing areas as low-, medium- and high-prevalence. The Rapid Assessment of Geographical distribution of Bancroftian filariasis (RAGFIL) is one of the most notable methods, developed in the 1990s (8). RAGFIL uses a sampling grid of 50x50 km and samples 50 adult males for the presence of hydroceles and antigen presence using ICTs and ties them to global positioning system (GPS) coordinates in order to produce an accurate distribution of disease patterns. Another method,

the lot quality assurance sample (LQAS), can be utilized for mapping purposes (9). In this approach a set number of individuals are randomly selected for testing until either the pre-specified number of infections is observed or the maximum number of individuals in the test-lot is reached. This approach is useful when trying to identify areas for MDAs but does not provide a comprehensive estimate of prevalence of disease.

Low-prevalence areas provide a valuable testing environment and are a growing area of concern post-MDA. Cases are few in number and sampling for such cases can often be challenging. It can be difficult to provide the proper amount of resources necessary to get an accurate estimate of the level of transmission in a low-prevalence setting. One must carefully consider the best way to sample. Is it better to find the few cases by performing a simple random sample, knowing that it may take the sampling of quite a few individuals to find any cases? Or should one continue with the standard lot quality assurance sample (LQAS) method which typically uses a convenience sample of schoolchildren? Or is there a better way to look at previous sites of transmission in order to sample the most likely candidates? Areas showing prevalence <1% are said to be areas of low transmission where MDAs are not necessary and transmission is not considered to be a threat. However, not all studies have shown low overall prevalence to be the same as low levels of transmission. Microfoci of transmission may exist in settings where overall antigen-prevalence is low. The concern is that persistent

antigenemic or microfilaremic areas are at risk for re-occurrence should MDAs be withdrawn prematurely.

Whether or not treatment is needed in low-prevalence areas is an important question. The fear is that even a small reservoir of infection can cause a threat of resurgence of the disease, and a non-protected community might be more at risk for such resurgence. Thus, balancing the costs and benefits for drug treatment in low-prevalence areas is a continued question and as of yet, there is no firm conclusion. A study in Egypt suggests that single mass treatment with DEC may be sufficient to stop transmission in low infection intensity areas (demonstrated by a 84% decrease in Mf after only one dose of DEC) (10)-although it should be noted that this study was of a limited sample size. A more recent study (2009) in India, however, addressed the prolonged persistence of *W bancrofti* even after MDAs for up to 20 years (11). MDAs of DEC were administered 1982-1986 bringing the Mf prevalence from 4.49% to 0.08%, in the nearly 20 year period following Mf prevalence persisted (0.03-0.43%) in the population when tested annually. There were no circulating filarial antigens (CFA) in children ages 1-20. It was theorized that this could be due to prolonged fecundic life-spans of adult parasites for which the DEC treatment failed to clear the infection completely (11). This corresponds to other research where, in the absence of incoming larvae, the adult worms that survived treatment may have lived longer than was originally thought (12). The remaining question is: does a small prevalence of remaining worm density still pose a risk to the entire population?

To help address this question we also need to look at the transmission intensity. Low-transmission intensity may reflect the inefficiency of the transmission of filariasis via the mosquito vector, it also depends on multiple factors including worm load and biting frequency (10). Unfortunately these are difficult events to measure accurately. Although attempts have been made, it is yet unknown if parasite density increases or decreases the survival and transmissibility of the parasite (13) and further research is needed in order to correlate transmissibility to rates of infection, particularly in low-prevalence areas. Regardless of MDAs it is obvious that increased surveillance will be of particular need during the road to elimination. Surveillance may need to proceed on both large and small scale to judge both the overall effect of MDAs on the population and the more focused small scale transmission patterns from the remaining positive individuals.

Although epidemiologic studies are the optimal method of determining risk they are also expensive to perform and require significant amounts of time and previous knowledge. Probabilistic modeling techniques have been used to bridge the gap between theory and actual studies. Validated models have been used extensively to identify communities possibly at risk for LF transmission and have attempted to relate certain indicators which might be difficult to measure (such as biting rates, transmission potentials, or immune response) as well as more abstract indicators (such as transmission indexes and composite risks) to the incidence of disease (2, 14). However, models also do not allow for the interrelation and

interaction between variables which could constitute actual risk. Full transmission models can be used to relate rate of transmission to intensity and distribution in human populations including EPIFIL and LYMFASIM (15). Both have lead to conclusions that it is possible to eliminate LF by yearly MDAs but is highly dependent on the coverage, pre-MDA prevalence and the marcofilaricidal effects of the drugs (13). The current WHO recommendations dictate that all areas with greater than 1% prevalence receive 4-6 rounds of MDAs with at least 60-70% compliance. Implications of the above research may lead to the extension of the number of required MDAs. The above models have suggested that the number of necessary MDAs may be as many as 12 to bring to elimination (0.5% prevalence) (13). Enumeration of the MDAs may also depend on whether the area had previously low or high endemnicity. Grady et al. show from a study in Haiti that in low-antigenemia settings fewer than 5 MDAs may be needed, but for areas with high antigenemia may require more (16).

Even though the majority of the disease burden of LF is in sub-Saharan Africa and Southeast Asia there at least 4 countries reporting active transmission of LF in the Americas including Brazil, the Dominican Republic, Guyana and Haiti, with roughly 90% or the disease burden in Latin America and the Caribbean (LAC) found in Haiti (17). Haiti is a particularly vulnerable area to diseases like LF which are highly associated with poverty and poor living conditions. Roughly 53% of Haiti's residents live below the international poverty line making them highly susceptible to disease (17). MDAs have been ongoing in areas of Haiti experiencing

>1% Mf since 2000, while others did not receive MDAs until very recently. Haiti is a small, but diverse country and since it is one of the poorest areas in the Western Hemisphere it provides a unique research setting for LF.

In 2001 mapping began in Haiti using schoolchildren as the primary sample for defining in the prevalence of LF regionally and nationally using the lot quality assurance sampling (LQAS) method (18). Blood samples were taken from 6-11 year olds, during school hours, in 133 communes across Haiti. The original intent of the mapping was not to gather an accurate estimate of the prevalence of LF, but to identify those communities requiring MDAs as per the WHO guidelines (18). A total of 22,365 children were tested identifying 117 communes requiring MDAs (18). Original prevalence assessments showed ranges from 0-45% prevalence among the tested children (18). In general, higher levels of transmission were associated with coastal regions (see appendix I, Figure 2) and other more macro-scale determinants have been assessed for risk of transmission.

Distance to water sources, urban/rural spread and soil type risk factors are more associated on a macro-scale and can be applied to the risk experienced by entire populations. Differences between risks associated with individuals within a community are not fully understood and are far more difficult to elucidate. Such episodes of heterogeneity can be difficult to identify and are the crux of epidemiologic research. Heterogeneity may, therefore, be considered on two scales: the macro and the micro. Macro-scales are good for prioritizing areas of intervention and can incorporate the use of traditional geospatial mapping

techniques, but they are limited in their applicability. Much of the current research addresses how communities may be at risk due to their proximity to water, elevation or soil type etc. Micro-scale heterogeneity can be used to determine factors affecting an individual's risk of disease and research in this area is greatly lacking.

Proximity to cases becomes of particular interest as communities see fewer and fewer instances of new disease and different studies have made separate conclusions surrounding the implied risk. For instance, a recently published article from Brazil details the risk assessment of family and neighbors of an infected patient in a non-endemic area (19). In a post-hoc analysis all 334 neighbors tested negative with thick blood smears and found no infection in the family. The individual had low parasite load and even though he had been living in the non-endemic area for 10 years he did not seem to pose a significant risk for transmission, as no one in the vicinity had become infected.

More in-depth studies regarding proximity to cases have been conducted by Washington et al. This study took place in an area of low-prevalence of infection where transmission was not considered to be high. Individual houses were mapped and were categorized as low, medium and high positivity for IgG1 using the average value per household in the model. The primary interest was distance to nearest residence of antigen-positive individual in 2000. They determined that for every 10 meter increase in distance from an antigen-positive case there was a 5.6% decrease in IgG1 antibody levels when controlling for age, gender and treatment

status (p=0.04) (20). Results further suggested that IgG4 is more associated with current infection and IgG1 may be more associated with exposure status. This study has provided preliminary evidence that there is a decrease in antibody levels with greater distance from an antigen-positive individual; however, it has a limited focus to only antibody responses and thus may not correspond to risk of infection, only exposure. Nonetheless, this study has shown that even in low-prevalence settings distance to cases is significant, and could have implications for the measures of elimination and the number of MDAs required.

New efforts are being made to produce a manageable end-game plan for those few countries nearing elimination. Some of the questions still lingering include how many MDAs are necessary? Is <1% prevalence adequate? What types of surveillance post elimination are necessary? And does low-prevalence necessarily correspond to low transmission? These questions, among others were recently addressed at the annual Global Alliance for the Elimination of Lymphatic Filariasis meeting this year. While new criterions have been addressed there are yet questions to be answered.

Chapter 2: Manuscript

Abstract:

Lymphatic filariasis (LF) is a filarial infection associated with severe morbidity endemic in over 80 countries, including Haiti. Yet, LF is one of a handful of infectious diseases said to be nearing global elimination. Many populations endemic for LF have seen decreased prevalence over the last decade as availability and use of mass drug treatment has increased. In progression towards global elimination, the World Health Organization (WHO) recommends that any area with prevalence greater than or equal to 1% should receive mass drug administration (MDA) for at least five consecutive rounds in order to interrupt transmission. It is believed, though not proven, that areas of low-prevalence pose little risk for continued transmission of LF. Five low-prevalence communes identified in the original nation-wide mapping in 2001 were utilized in this study: Grand Goâve, Hinche, Moron, St. Louis de Sud and Thomazeau. An initial evaluation of schoolchildren was performed in each commune to help identify antigen-positive children, who could be sources of transmission within their communities and act as focal points for the subsequent community survey. Two case definitions were employed to identify these sources: index cases (antigen-positive) and antigen-positive ELISA-based autochthonous (AEA) cases (confirmed infections known to have been locally acquired). Global Positioning System (GPS) coordinates and immunochromatographic tests were collected on approximately 1,600 persons of all ages in the five communes. The likelihood of antigen-positive cases being in proximity to index and AEA cases was evaluated using multivariate

regression techniques and Bernoulli cluster analyses. Community surveys revealed higher antigen prevalence in three of the five communes than was observed in the original mapping effort. Regression techniques identified a statistically significant increased likelihood of being antigen-positive when living within 20 meters of either index or AEA cases when controlling for age, gender, and commune and spatial clustering of antigen-positive cases was observed in some, but not all communes. Such results indicate that localized transmission was occurring, even in low-prevalence settings. These results suggest that more robust surveillance may be needed in order to detect and extinguish lingering sources of transmission.

Introduction:

Lymphatic filariasis (LF) is one of 13 neglected tropical diseases (NTDs) known to chronically infect some of the worlds' poorest individuals (1). While LF has been shown to be endemic in over 80 countries world-wide, it is one of only six diseases in 1993 which were deemed to be eradicable (2). There are three species of nematodes known to cause lymphatic filariasis: *Wuchereria bancrofti, Brugia malayi and Brugia timori*, each with its own unique geographic domain. LF is found world-wide, but is most prevalent in sub-Saharan Africa and Southeast Asia. Mosquito vectors associated with LF include *Culex, Anopheles, Aedes,* and *Mansonia.* Adult worms promote lymphatic dysfunction, interfering with the proper exchange of fluids throughout the body causing lymphedema and elephantiasis, well-known results of LF. While LF is not fatal it is extremely

debilitating, disfiguring and holds a terrible stigma for those affected. Symptoms can be managed and progression halted, but the damage to the lymph tissue is not reversed by community treatment and often first presents years after the filarial infection.

Since LF was made a priority by the WHO in 1997 there has been much progress in the control and elimination of LF across the globe. In 2000, the WHO developed the Global Programme for the Elimination of Lymphatic Filariasis (GPELF), which set forth the goal to eliminate LF by 2020. The definition of elimination used by the WHO includes microfilaria (Mf) prevalence <1% and evidence that there is no new parasitic infection in the community (observed, for example, by 5-year cumulative incidence in children born after the start of Mass Drug Administration (MDA) less than 1 per 1000 children). A "two-pillar" approach has been implemented for the control and elimination of LF that focuses on the interruption of transmission through MDAs and limiting the disability caused by infection by introducing morbidity management programs. MDAs use antifilarial drugs, such as diethylcarbamazine (DEC), to kill circulating microfilaria, thus preventing them from being taken up by mosquitoes and continuing transmission.

Mapping of lymphatic filariasis is particularly helpful in the identification of areas requiring MDAs and allows for the tracking of progress towards elimination. As of 2009, 68 of the 81 endemic countries had completed mapping of LF (7). Tests of antigenemia, including immunochromatographic (ICT) and Og4C3 enzyme-linked immunosorbant-assay (ELISA), are generally thought to be the easiest and

cheapest measures of prevalence for field-based tests, such as those performed during mapping activities. Rapid mapping has been a key step in elimination and several methods have been utilized in the past categorizing areas as low, medium and high prevalence. The Rapid Assessment of Geographical distribution of Bancroftian filariasis (RAGFIL) is one of the most notable methods, developed in the 1990s (8). RAGFIL uses a sampling grid of 50x50 km and samples 50 adult males for the presence of hydroceles and antigen presence using ICTs, and ties them to GPS coordinates in order to produce an accurate distribution of disease patterns. However, it requires a large sample size to generate accurate numbers with less prevalent diseases. Several researchers have argued to forgo a simple random sample in areas of low-prevalence for a convenience sample in order to optimize the result return, while minimizing resources required. The standard lot quality assurance sample (LQAS) method which typically uses a convenience sample of schoolchildren to identify recent transmission of LF (9). In this approach a set number of individuals are randomly selected for testing until either the pre-specified number of infections is observed or the maximum number of individuals in the test-lot is reached. This approach is useful when trying to identify areas for MDAs but does not provide a comprehensive estimate of prevalence of disease.

Low-prevalence areas provide a valuable testing environment and represent a model for post-MDA surveillance. Areas showing prevalence <1% are designated as areas of low transmission, where MDAs are not necessary and transmission is

not considered to be a threat. However, it has not been well established that low-prevalence is the same as low transmission. Whether or not treatment is needed in low-prevalence areas has become an important question. The fear is that even a small reservoir of infection can cause a threat of resurgence of the disease, and a non-protected community might be more at risk for such resurgence. A study in Egypt suggests that single mass treatment with DEC may be sufficient to stop transmission in low infection intensity areas (10). A more recent study (2009) in India, however, addressed the prolonged persistence of *W bancrofti* following 20 years of MDAs, though at levels <0.5% (11). It was theorized that this could be due to prolonged fecundic life-spans of adult parasites, which the DEC treatment failed to clear completely (11). Thus, balancing the costs and benefits for mass drug treatment in low-prevalence areas is a point of consideration and as of yet, there is no firm consensus.

Haiti holds 90% of the LF disease burden in Latin America and the Caribbean (LAC) (17). In 2001 mapping began in Haiti using schoolchildren as the primary reservoir for looking at changes in prevalence of LF regionally and nationally (18). The mapping was intended to identify communities requiring MDAs, as per the WHO guidelines, and prevalence ranged from 0 to 45% among 6 to 11 year olds in the test population (18) and MDAs were applied accordingly. The communes in this study were originally labeled as low-transmission areas with prevalence <1%.

Antigen-positive children identified in a LQAS of schoolchildren were used as known carriers of LF in their communities. They served as centralized points in the following community survey in which households were mapped with Global positioning System (GPS) coordinates and a subset of habitants of various ages were tested for antigen-status. The analysis was designed to determine if active transmission of LF occurred in these settings and if infection prevalence exceeded the 1% trigger for MDA in some microfoci.

Methods:

Low-prevalence study sites:

In 2001 nation-wide filarial mapping was performed utilizing 100-250 schoolchildren between the ages of 6 and 10 years of age across all Haitian communes, which are administrative sub-units of the ten departments. These children were tested by ICT with blood drawn using the finger-prick method. Based on prevalence data specific communities (≥10% prevalence) were targeted for MDAs. Our evaluation focused on low-prevalence areas resulting in the identification of 5 communes with prevalence <1% for further research in our study: Grand Goâve (0.8%), Hinche (1.0%), Thomazeau (0.6%), Moron (0.8%), and St. Louis de Sud (0.4%).

School surveys and serologic testing:

Within each of the communities of interest, five to seven schools were chosen to receive additional ICT testing. These public and private schools were in urban and rural areas, and were representative of the area. Blood samples were collected, in accordance with CDC, Ste. Croix Hospital and University of Notre Dame internal review board (IRB) protocols, from students at the time of ICT testing and were used to verify antigen status by Og4C3 ELISA methods (current gold standard for antigen testing). Based on the school ICT testing results questionnaires were given to all children who were antigen-positive. The questionnaires were mainly designed to identify autochthonous cases—defined as those individuals who conclusively acquired the infection in the town of origin as determined by a series of questions about their travel and living situations in the last 5 years. The questionnaire also elucidated potential risk factors and potential confounders such as urban/rural living, access to running water, latrine usage, and socioeconomic status.

Case selection:

Five to eight antigen-positive children were chosen from each community to represent the index cases for that area. Index cases were those identified as antigen-positive by ICT in the school survey. ELISA tests were done for confirmatory testing after the initial survey. Index cases were not necessarily autochthonous, however. A second, more stringent case definition was applied using individuals with positive ELISA values and who were defined as autochthonous based on their answers to the survey. These individuals were

referred to as antigen-positive ELISA-based autochthonous (AEA) cases. Both index and AEA cases were used as the central points from which distance was measured for the community survey. Index cases were chosen to sample communities that were geographically diverse. Households of index cases were placed at the center for each testing radius. All neighboring houses within the test radius were mapped, a subset of which were tested for antigen status.

Community survey:

In order to generate an accurate geographical representation of the test area, households within the test radius were mapped using GPS TerraSync. Circles of 50-75 meters were used in more densely populated urban areas, and circles of 100-250 meters were used in sparsely-populated rural settings. After index and AEA cases were identified all consenting members of such houses, and a systematic random sample of the neighboring households were selected for ICT testing. In an effort to test 100 persons per community, approximately 20 households were chosen, estimating 5 persons per household (unpublished data). To select these 20 houses, the total number of houses in the zone was divided by 20 to determine the sampling interval. Houses were selected from a numbered list using a randomly selected starting point and this sampling interval. The methods of blood/serum collection, processing and testing were the same as the school survey previously described. Antigen-positive persons were treated with 6mg/kg DEC and administered a questionnaire as in the school survey. The community survey evaluated a total of 1,633 persons. For our study subjects were selected if

they had not been previously defined as an index case in the school study, received an ICT test result, and GPS coordinates were able to be mapped for their household (n=1290).

Data analysis:

Data were analyzed using SAS 9.3 (Cary, NC, USA), Epi Info 6 (CDC, Atlanta, USA) and ArcGIS (v. 9.3.1, Environmental Systems Research, Inc., Redlands, CA, USA). Univariate, Mantel Haenszel chi-square and logistic regression techniques were employed. The multivariate logistic regression models the outcome of a +/- ICT result and the primary exposure of distance to index and AEA cases, broken into ordinal categories of distance, controlling for age, gender and commune.

The outcome of interest for this analysis was antigen positivity as denoted by the ICT results performed in the field or those subsequently confirmed with ELISA tests performed in a laboratory. Two separate case definitions were employed in this analysis informing two mutually exclusive exposures. The index case definition was more inclusive, only requiring a positive ICT or ELISA test. Index cases would therefore serve as potential, but unconfirmed, reservoirs of infection. Conversely, the AEA cases were limited to those confirmed by ELISA results and who were deemed to be autochthonous by a detailed account of residence in the survey, which serve as proof of localized transmission. The exposure of interest was the distance from each person tested to the nearest index or AEA case. In order to determine the ordinal categories which best represent the

distance, we performed a sensitivity analysis for dichotomized distances of 10, 20, 40, 80 and 160 meters. Analysis of distance when using the AEA case definition revealed no antigen-positives in the 59-99 m group, so the categories of 59-99 and 100+ meters were combined into a 60+ meter group, used as the referent for the crude and multivariate regression analyses.

Potential confounders and effect modifiers, including age, gender and commune, were also considered based on previous literature and anticipated heterogeneity among the communes. For the purpose of modeling, age was dichotomized into <15 years and ≥15 years.

A spatial cluster analysis was performed on mapped households in the four communes recording antigen positivity. The analysis tested the spatial clustering of antigen-positive persons (excluding index cases) through the use of a Bernoulli model in SatScan, version 9.1.1. A separate cluster analysis was performed for each of the four communes to better elucidate micro-clusters. Both general and isotonic simulations were performed on the commune-specific data, the latter of which accounts for the inverse relationship between risk and distance from the center of the cluster. This type of simulation holds biological plausibility in representing the transmission patterns of vector-borne diseases.

Results:

Of the 2,639 children tested in the initial school survey 64 (2.7%) were antigen-positive (see Table 1). The school survey was used as a direct guide for selecting the testing areas of the subsequent community survey beginning in 2003. Table 2 shows the characteristics of the study population. A broad range of ages were covered in the study population ranging from 2 to 90 years old (average age is 24). The overall study population demonstrated an increase in antigen-positivity from young children (0 to4 years old) to older children (ages 5 to 9 years old) after which the level of antigenemia was maintained for the remaining age groups (see Figure 1). Females were only slightly more represented in the test populations, but this difference was not statistically significant. Urban populations, on the other hand, were not well represented as the majority of the communes were determined to be rural in nature. Comparisons of antigen prevalence were performed for each variable showing the distributions of each, of which, only distance from index case was significant (p=0.0044), see Table 2.

The average distance from an index case for the entire test population was 237 m (range 0-4977 m), whereas the average distance from an AEA case was 1440 m (range 0-4977 m). The distribution of these distances was skewed by the observation of large distances from AEA or index cases in Hinche. One index case which identified a sampling area was unable to be mapped with GPS, thus creating a larger distance for individuals in that sampling cluster than would normally have

occurred. Since there are so few AEA cases the average distance of each household to the nearest AEA case increases considerably. The sensitivity analysis concluded that the distance of 20 meters from the index case was the most significant (see Table 3). Furthermore, antigen positivity is most highly represented in the distance from index case less than 20 m, with decreasing antigen prevalence as distance increases (see Figure 2).

Index case results:

The school survey was unable to identify any antigen-positive children in Moron among those with geospatial information, and thus all points within the Moron commune were excluded from further analysis. Among the remaining communes, antigen prevalence was highest in Grand Goâve (4.35%), and lowest in St. Louis de Sud (0.82%), excluding index cases.

Crude odds ratios were calculated to evaluate the odds of being antigen-positive compared with antigen-negative across the individual covariates: distance, age, gender, locale and commune (see Table 4). Distance was organized into four categories: <20 m, 20-59, 60-99 and 100+ meters measuring distance from the individual's household to the nearest index case. A distance of less than 20 m produced a prevalence odds ratio of 4.99 [95% CI 1.60, 15.51] when compared with distances of 100 m or more from an index case. Communes of Grand Goâve (cPOR 2.38 [95% CI 0.94, 6.03]) and Hinche (cPOR 2.17 [95% CI 0.83, 5.67]) showed increase odds of antigen positivity, although these results were not statistically significant when compared with results from Thomazeau.

Multivariate logistic regression techniques were applied and evaluated for collinearity, interaction and confounding, and the final model is presented in Table 5 where the exposure of interest is distance from index cases. The odds of positive antigen status among persons living within 20 meters of an index case is 5.41 [95% CI 1.64, 17.83] times the odds of positive antigen status among persons living at 100 meters or more from an index case, when controlling for age, gender and commune. The communes of Grand Goâve and Hinche showed significantly higher prevalence odds ratios (5.72 [95% CI 1.26, 25.90], and 7.17 [95% CI 1.53, 33.50] respectively) when evaluated at the 5% significance level.

The Bernoulli model analyzed spatial clustering on cases and non-cases from a total of 319 households, each with an average of four people tested. Results shown in Table 6 demonstrated statistically significant clustering of cases in Hinche and Thomazeau, when evaluated at the 5% significance level in both the general and isotonic Bernoulli analyses. Examples of clustering can be seen in Figure 3.

AEA results:

The parallel analysis using the AEA case definition determined that there were no AEAs in the initial school survey in Moron and St. Louis de Sud, which were therefore excluded from further analysis. Among the remaining communes, antigen prevalence was highest in Hinche (4.44%), also high in Grand Goâve (3.76%) and lower in Thomazeau (1.94%).

Crude odds ratios were calculated for the individual variables of distance, age, gender, locale and commune (see Table 7). A distance of less than 20 m produced a prevalence odds ratio of 6.76 [95% CI 2.31, 19.78] when compared to distances of 60 m or more from an AEA case was found to be statistically significant at the 5% significance level. Communes Grand Goâve (cPOR 1.98 [95% CI 0.71, 5.52]) and Hinche (cPOR 2.36 [95% CI 0.84, 6.58]) showed increased odds of antigen positivity when compared to results from Thomazeau in the crude analysis, though neither were statistically significant.

Multivariate logistic regression techniques were additionally applied to this case definition, were evaluated for collinearity, interaction and confounding and the final model is presented in Table 8. The odds of positive antigen status among persons living within 20 meters of an AEA case was 6.70[95% CI 2.02, 22.21] times the odds of positive antigen status among persons living at 60 meters or more from an AEA case when controlling for age, gender and commune. The communes of Grand Goâve and Hinche showed slightly higher odds of being ICT-positive when compared to Thomazeau; and were statistically significant when evaluated at the 5% significance level. Spatial cluster analysis was not performed using this case definition as it was assumed that the clustering previously observed in the commune of Hinche would still apply to this case definition as it is a subset of the index case population.

Discussion:

School survey:

The original mapping for Haiti carried out in 2001 identified the communes of Grand Goâve, Hinche, Moron, St. Louis de Sud and Thomazeau to be areas of low antigen prevalence (<1%). As transmission of lymphatic filariasis was presumed to not be occurring, it was accepted that mass drug administrations were not required. A subsequent school survey was conducted to determine if additional testing in schools and follow up testing in communities of antigen-positive children could identify foci of transmission that were not picked up in the initial national survey. The results from our survey showed higher than expected (>1%) antigen prevalence in all communes except for Moron and St. Louis de Sud (see Table 2). A questionnaire was given to the children who presented with an ICT-positive test. It contained a series of questions intended to elucidate the areas in which these children had lived in order to determine if the infection was acquired locally, identifying them as autochthonous cases. Of the 64 children who tested antigen-positive complete questionnaire data were available for only 23. A total of 12 autochthonous cases were identified in all 5 communes through the use of the school survey, meaning that more than half (52%) of the children who answered the questionnaire had acquired their infection locally in Grand Goâve, Hinche and Thomazeau. These conclusions provide evidence that transmission of LF is occurring in settings that did not previously qualify for MDAs based on the 2001 national survey. These results were shared with the Haitian Ministry of Health leading to the decision to carry out MDAs across all Haitian communes, independent of the initial mapping results.

Haiti is one of a very small number of countries that have carried out a re-assessment of low-prevalence areas. It is not clear whether re-assessments in other countries would similarly lead them to re-consider decisions to not carry out MDA in settings originally judged to be low-prevalence. The decision by the Haitian Ministry of Health might be judged as conservative; on the other hand, there is a dearth of evidence on the long term persistence of transmission in low-prevalence settings.

Community survey:

There was statistically significant spatial clustering of antigen-positive cases in Hinche and Thomazeau which suggests that transmission might be occurring in low-prevalence areas among people in close proximity to one another. This implies that risk could be associated with the distance to existing reservoirs of infection. This relationship was further analyzed with the use of the logistic regression to model the affect of distance from index and AEA cases on ICT status. The model demonstrated a statistically significant increased likelihood of having a positive ICT result when residing within 20 meters of a case, controlling for age, gender and commune, further substantiating the claim that proximity to these microfoci, of infection may be associated with the risk of acquiring LF. Since infection is circulating in these microfoci, one might consider the micro-environment to be of substantial interest and a potential source of effect modification and confounding, including such factors as socioeconomic status, distance to fresh-water sources and nearest latrines, and characteristics of local mosquito populations. However,

due to overwhelming poverty of the Haitian people in these primarily rural communities, it is unlikely that much heterogeneity would be observed in this setting; nevertheless, these might be important factors to consider in other study areas. Our results were further substantiated by the increased odds of antigen positivity observed within 20 meters of an antigen-positive ELISA-based autochthonous (AEA) cases in the parallel analysis. These statistically significant results provide direct proof of local transmission in these three low-prevalence communes of Haiti.

Risk associated with proximity to cases becomes of particular interest as communities see fewer and fewer instances of new disease, and different studies have made separate conclusions regarding the implied risk. For instance, a recently published article from Brazil details the risk assessment of the family and neighbors of an infected patient in a non-endemic area (19). The individual had low parasite load and, even though he had been living in the non-endemic area for 10 years, he did not seem to pose a significant risk for transmission, as no one in the vicinity had become infected. However, this study was only observational to one individual and therefore may not be generalizable to the overall population.

Washington et al. further addressed the risk related to distance from antigen-positive cases on the exposure to LF through an analysis of changes in antifilarial antibodies (20). This low-prevalence study determined that for every 10 m increase in distance from an Ag-positive case, there was a 5.6% decrease in IgG1 antibody levels, when controlling for age, gender and treatment status ($p=0.04$)

(20). These observations however, coupled with our present study indicate substantial risk with spatial proximity to an antigen-positive person in both exposure as well as acquisition of LF and clustering may play a substantial role in transmission dynamics. Such results could have implications for end-stage of LF elimination programs requiring increased emphasis on case detection to promptly identify persons at risk.

The logistic regression model also produced significant results (see Table 5), suggesting a difference in the number of ICT-positives among the various communes, using the index case definition. Results such as these might indicate heterogeneity among the communities. Since each of the five communities is in different parts of Haiti, it is possible that there are differences in the transmission of LF due to different physical environments. Table 9 shows some of the differing characteristics of each community, which might contribute to the heterogeneity of the commune environments. A sensible explanation of why certain communes are statistically associated with ICT status might be that a high population, either of vectors or humans, may be more compatible with transmission of LF. We did not, however, collect data on mosquito densities for this study. Human population densities are recorded in Table 9 in two forms: one for the commune-wide reported density, and the other for this study-specific calculation which is based on the study population and the specific geographic area which was sampled. This finding suggests that since the communes of Hinche, and particularly Grand Goâve have higher calculated population densities, when compared to St. Louis de Sud

which might correspond with higher rates of transmission, although this conclusion would not hold if considering the commune as a whole. Future studies might look at the micro-environment of study participants on an individual basis to better address possible heterogeneity.

Limitations:

This study is only a preliminary analysis of the prevalence associations in these 5 communes in Haiti in 2003. Results are preliminary and relate to the prevalence effects in only these 5 communes in Haiti. This should be kept in mind for broader implications of these data. Risk could not be established in this cross-sectional study, and we suggest a cohort study be generated in order to confirm these results. The cross-sectional study design also does not allow for chronology to be established so there is no way to determine if cases identified in the school survey were infected before or after their ICT-positive neighbor. Thus, we could not determine the actual reservoir for transmission. ICT results, while generally highly specific, are not considered the most accurate test for LF infection. Og4C3 ELISA results would better quantify the presence of the antigens; however, due to financial and logistical concerns for field work, ICT results were utilized for all participants in this study. Transmission rates would be the best measure of continued transmission; however, they cannot be calculated without the input of entomological evidence including biting rates and infection levels in mosquitoes. We used antigen positivity as an indicator of transmission in lieu of the tedious and expensive acquisition of such entomologic data.

Since this study was carried out in low-prevalence settings there were few persons found to be antigen-positive, though more than were expected. This is a challenge of sampling in a low-prevalence setting rather than population-wide surveillance—it does decrease the power available to the analysis by having only 33 non-index ICT-positives with which to work. Similarly, there were only 27 index and 10 AEA cases identified from the school survey that were subsequently used for this analysis. Although some of these index cases are autochthonous, not all met the qualification based on antigen status and history of living in the area; in other cases, parents were not available to confirm the residential histories of antigen-positive children. Index cases provide only the opportunity to look for other cases, where as positive autochthonous cases are proof of local transmission. In order to evaluate the exposure of interest, we required that GPS coordinates be available, in addition to ICT results, all of which were not able to be matched to test results. A final limitation is that the sampling technique for the community survey focused on the index case as the epicenter of the sampling and tested roughly 20 neighboring households, perhaps creating bias in the geographic dispersion of households, as they were already clustered. Therefore, it is possible that the clustering observed by the non-index antigen-positives is an artifact of the sampling method in which sampling patterns were designed to operate within the prescribed radius of the index case. Since the sampling technique required that households be surveyed within a set radius of cases, geographic dispersion was not fully evaluated. It is possible that cases identified at farther distances would have

decreased the likelihood ratio of cases within a set radius making the observed clustering less significant.

Conclusions:

There has been much controversy about what processes should be employed when nearing stages of elimination of a transmittable disease, since there is little to no precedence for the end-stage policies, procedure and methods of surveillance. Thus, studies such as this one in low-prevalence areas are particularly important for informing and shaping the end-game plan for all diseases nearing elimination.

It is important to note that this study has demonstrated that transmission, using antigen prevalence as a proxy, is still occurring in areas that had previously been categorized as areas with low risk of transmission suggesting that areas of low-prevalence may not be equated with areas without transmission risk. This may lead to the reconsideration of the current 1% cut-off for mass drug administrations. The country-wide mapping techniques in 2001 revealed a prevalence of <1% for all five communes, and this study returned prevalence values ranging from 0 to 5.6% in the school survey and 0 to 4.35% in the community survey.

Index and antigen-positive ELISA-based autochthonous cases indicate that transmission is occurring at the level of microfoci. Determining that an individual is a potential risk to the persons in close proximity may change the way we approach the treatment of isolated cases. We might employ a ring technique,

similar to that used in the eradication of smallpox, where detection of a case necessitates that everyone within close proximity to that case be treated via prophylaxis to better reduce the chances of transmission to a naïve host. Since our analysis revealed that living within 20 meters of an index case significantly increased the likelihood of being antigen-positive, we would suggest that individuals dwelling at least within 40 meters of a confirmed case should be tested and treated presumptively.

This study focused on the use of a convenience sample of children to identify antigen positive children as indicators of potential microfoci. While these are smaller subsets of the population, they may better capture accurate prevalence values than the currently used technique. The current mapping technique recommended by WHO, RAGFIL, uses a sampling grid of 50x50 km and samples 50 adult males for the presence of hydroceles and antigen presence using ICTs. This study may demonstrate that evaluation prevalence using a convenience sample of children is not only easier to implement, but may also return more accurate results. Even if these results are higher than the actual prevalence, one could argue that when working to eliminate a disease, it would be better to utilize a method that would be more sensitive, rather than specific. The evaluation of the schoolchildren would do just that. Furthermore, utilizing schoolchildren as indicators of the prevalence within the general population is a better demonstration of newly acquired infections. New strategies for surveillance

coupled with better diagnostic tools will lead to more comprehensive identification of cases which can subsequently be controlled.

The techniques for surveillance might be better assessed using the prevalence of schoolchildren as well. In order to ensure the interruption of transmission, a higher level of sensitivity must be maintained. As there appears to be a continued reservoir of infection even after prevalence drops below 1% periods of surveillance should be increased in order to monitor present levels of antigen positivity. Ramaiah et al. reported residual microfilaria prevalence ranging from 0.03 to 0.43% in the population when tested annually over a period of 20 years post MDA (11). It is impractical to require a surveillance period of 20 years post MDAs; however, increasing the period of surveillance from five years to ten years might be necessary to ensure that transmission has indeed stopped or at least slowed to a point which cannot sustain the filarial lifecycle.

Campaigns to combat LF should be aimed at high levels of coverage during MDAs, which will include addressing any situations of systematic non-compliance, and should emphasize a multi-faceted approach to the prevention of LF. These strategies should include not only pharmacologic interventions, but also bednet distribution, vector control and continued education in order to make greater strides to eliminate this debilitating disease.

Table 1. Distinction of antigen positive, autochthonous and index cases from the school survey, 2001-2003, in selected low-prevalence areas of Haiti*

	Antigen status			ELISA positive, autochthonous determination			Index case
Commune	N tested	ICT positive	ELISA positive	Yes[1]	?[2]	No[3]	
Grand Goâve	430	24 (5.58%)	14 (3.26%)	7	1	1	7
Hinche	592	21 (3.55%)	11 (1.86%)	4	0	2	6
Moron	411	0 (0.00%)	0 (0.0%)	0	0	0	7
St Louis du Sud	466	8 (1.72%)	3 (0.64%)	0	0	3	5
Thomazeau	470	11 (2.34%)	5 (1.06%)	1	0	4	5
Total	2369	64 (2.70%)	23 (0.97%)	12	1	10	30

Yes[1] – Number of people who were determined to be autochthonous cases.

?[2] – Number of people who were possible autochthonous cases.

No[3] – Number of people who were non-autochthonous cases.

*Not all antigen-positive children (parents/guardians) were located or agreed to be answer the questionnaire.

Table 2. Characteristics of study population tested by antigen status in selected low-lymphatic filariasis areas of Haiti, 2003*

Variable	Total n	Antigen positive percent of total (n)	p-value**
Distance from index case(m)			0.0044
<20	217	5.99% (13)	
20-59	413	1.94% (8)	
60-99	343	2.33% (8)	
100+	317	1.25% (4)	
Age (years)			0.7565
Age≥15	745	2.68% (20)	
Age<15	540	2.41% (13)	
Gender			0.7143
Male	545	2.75% (15)	
Female	742	2.43% (18)	
Locale			0.1693
Urban	202	3.96% (8)	
Rural	1088	2.30% (25)	
Commune			***0.0136
Grand Goâve	299	4.35% (13)	
Hinche	276	3.99% (11)	
Moron	98	0.00% (0)	
St. Louis de Sud	244	0.82% (2)	
Thomazeau	373	1.88% (7)	

*Total n may differ depending on the number of persons responding to each variable.

**p-value was determined using a chi square analysis with a significance of $p<0.05$.

***p-value was determined using Fisher's exact methods with a significance of $p<0.05$.

Table 3. Crude sensitivity analysis for distance from index case (m) on antigen status in selected low-prevalence areas of Haiti, 2003 (n=1290)

Classification	cPOR	95% CI	p-value*
<10	1.79	(0.73, 4.41)	**0.2554
≥10	1.00 (ref)		
<20	3.36	(1.64, 6.85)	0.0004
≥20	1.00 (ref)		
<40	2.39	(1.19, 4.78)	0.0113
≥40	1.00 (ref)		
<80	1.58	(0.73, 3.43)	0.2423
≥80	1.00 (ref)		
<160	3.07	(0.42, 22.68)	**0.3544
≥160	1.00 (ref)		

*p-value was determined using a chi square analysis with a significance of $p<0.05$.

**p-value was determined using Fisher's exact methods with a significance of $p<0.05$.

Table 4. Crude odds ratios for covariates on antigen status with the index case definition in selected low-prevalence areas of Haiti, 2003*,***

Variable	cPOR	95% CI
Distance from index case (m)		
<20	4.99	***(1.60, 15.51)
20-59	1.55	(0.46, 5.18)
60-99	1.87	(0.56, 6.27)
100+	1.00 (ref)	
Age (years)		
Age≥15	1.12	(0.55, 2.27)
Age<15	1.00 (ref)	
Gender		
Male	1.14	(0.57, 2.28)
Female	1.00 (ref)	
Locale		
Urban	1.75	(0.78, 3.94)
Rural	1.00 (ref)	
Commune		
Grand Goâve	2.38	(0.94, 6.03)
Hinche	2.17	(0.83, 5.67)
St. Louis de Sud	0.43	(0.09, 2.10)
Thomazeau	1.00 (ref)	

*Total n may differ depending on the number of persons responding to each variable.

**Moron was excluded from further analysis because it showed no positive results for antigen status.

*** Confidence intervals were significant with a $p<0.05$.

Table 5. Final multivariate model for the effect of distance from index cases on antigen status controlling for the other variables in the model in selected low-prevalence areas of Haiti, 2003 (n=1187)*

Variable	POR	95% CI
Distance from index case (m)		
<20	5.41	**(1.64, 17.83)
20-59	1.45	(0.41, 5.13)
60-99	1.85	(0.54, 6.35)
100+	1.00 (ref)	
Age (years)		
Age>15	1.21	(0.58, 2.50)
Age<15	1.00 (ref)	
Gender		
Male	1.15	(0.56, 2.34)
Female	1.00 (ref)	
Commune		
Grand Goâve	5.72	**(1.26, 25.90)
Hinche	7.17	(1.53, 33.50)
St. Louis de Sud	3.16	(0.63, 15.78)
Thomazeau	1.00 (ref)	

*Moron was excluded from further analysis because it showed no positive results for antigen status.

** Confidence intervals were significant with a $p<0.05$.

Table 6. Cluster analysis resultsfor clustering of antigen positive households by commune in selected low-prevalence areas of Haiti, 2003, using SatScan, version 9.1.1*

General Bernoulli cluster analysis

	Most likely cluster			Total significant clusters	
Commune	**p-value****	**radius (km)**	**number of cases**	**number**	**range of radii (km)**
Grand Goâve	0.1370	0.01	3	0	NA
Hinche	0.0025	0.00	3	4	0-0.37
St. louis de Sud	0.5300	3.84	2	0	NA
Thomazeau	<0.0001	0.00	12	5	0.00-2.31

*Isotonic Bernoulli cluster analysis****

	Most likely cluster			Total significant clusters	
Commune	**p-value****	**radii for steps 1-3 (km)**	**number of cases**	**number**	**range of radii (km)**
Grand Goâve	0.1910	0.01	3	0	NA
Hinche	0.0056	0.00, 0.12, 1.01	10	2	0.00-1.01
St. louis de Sud	0.2380	0.70, 7.00, 7.02	2	0	NA
Thomazeau	<0.0001	0.00, 0.07, 5.83	16	2	0.00-5.83

*Moron was excluded from further analysis because it showed no positive results for antigen status.

**p-value was determined using a chi square analysis with a significance of $p<0.05$.

***The isotonic Bernoulli cluster analysis decreases the effect as distance from the center increases. This analysis is carried out in 3 steps with increasing radii.

Table 7. Crude odds ratios for covariates on antigen status with the antigen positive ELISA-based autochthonous case definition in selected low-prevalence areas of Haiti, 2003*'***

Variable	cPOR	95% CI
Distance from index case (m)		
<20	6.76	***(2.31, 19.78)
20-59	1.34	(0.48, 3.73)
60+	1.00 (ref)	
Age (years)		
Age≥15	1.08	(0.49, 2.37)
Age<15	1.00 (ref)	
Gender		
Male	1.17	(0.54, 2.57)
Female	1.00 (ref)	
Locale		
Urban	0.89	(0.89, 2.39)
Rural	1.00 (ref)	
Commune		
Grand Goâve	1.98	(0.71, 5.52)
Hinche	2.36	(0.84, 6.58)
Thomazeau	1.00 (ref)	

*Total n may differ depending on the number of persons responding to each variable.

**Moron and St. louis de Sud were excluded from further analysis because they showed no positive results for antigen status.

*** Confidence intervals were significant with a $p<0.05$.

Table 8. Final multivariate model for the effect of distance from antigen positive ELISA-based autochthonous cases on antigen status controlling for the other variables in the model in the selected low-prevalence areas of Haiti, 2003 (n=797)*

Variable	POR	95% CI
Distance from AEA case (m)		
<20	6.70	**(2.02, 22.21)
20-59	1.26	(0.44, 3.61)
60+	1.00 (ref)	
Age (years)		
Age>15	1.11	(0.49, 2.49)
Age<15	1.00 (ref)	
Gender		
Male	1.33	(0.60, 2.97)
Female	1.00 (ref)	
Commune		
Grand Goâve	1.30	(0.41, 4.09)
Hinche	2.14	(0.75, 6.16)
Thomazeau	1.00 (ref)	

*Moron and St. Louis de Sud were excluded from further analysis because they showed no positive results for antigen status.

** Confidence intervals were significant with a $p<0.05$.

Table 9. Commune environmental characteristics of selected low-prevalence areas of Haiti					
	Population density		Geographic and topographic characteristics		
Commune	Calculated*	Reported**	Elevation (m)	Climate	Water sources
Grand Goâve	959	250-500	7	scrub/forest	coastal, river
Hinche	30	100-250	228	cropland/pasture/forest	land-locked, rivers
St. Louis de Sud	6	250-500	9	scrub/forest	coastal
Thomazeau	28	100-250	29	savanna/pasture	Land-locked, <4km to lakes

*Population density was calculated in ArcGIS for the study geomapped houses in study area only.

**Population density for entire commune, as reported by ReliefWeb, 2008.

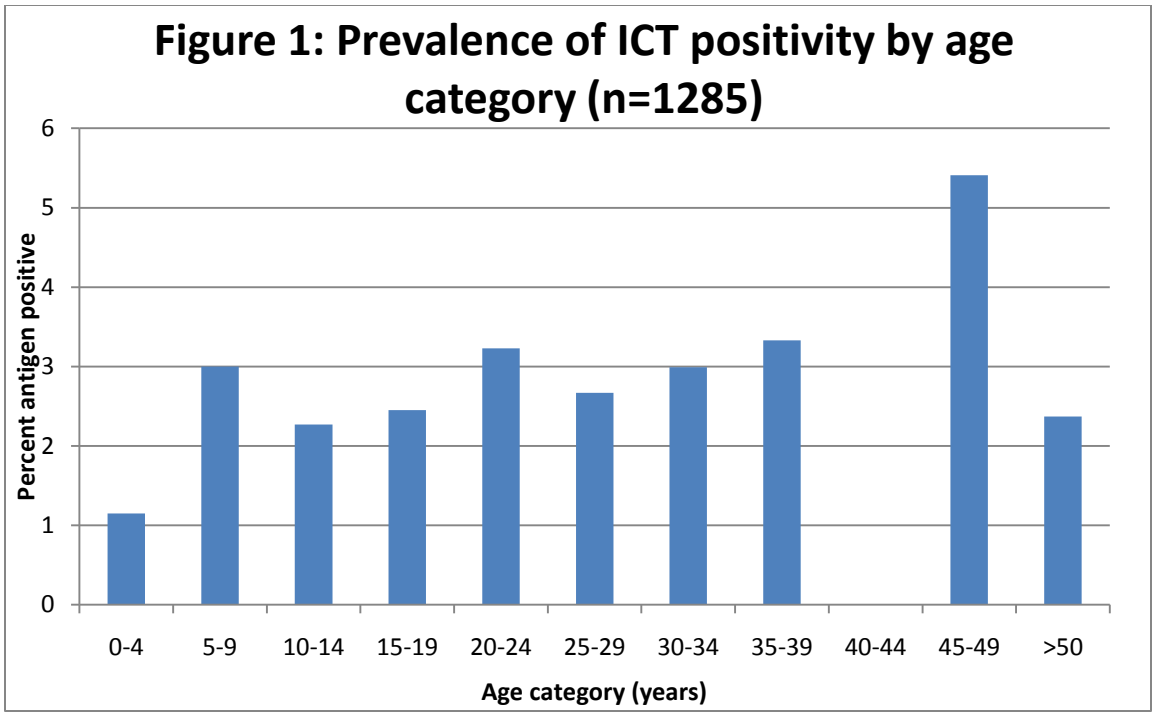


Figure 1: Prevalence of ICT positivity by age category (n=1285)
Percent antigen positive
0
1
2
3
4
5
6
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
>50
Age category (years)

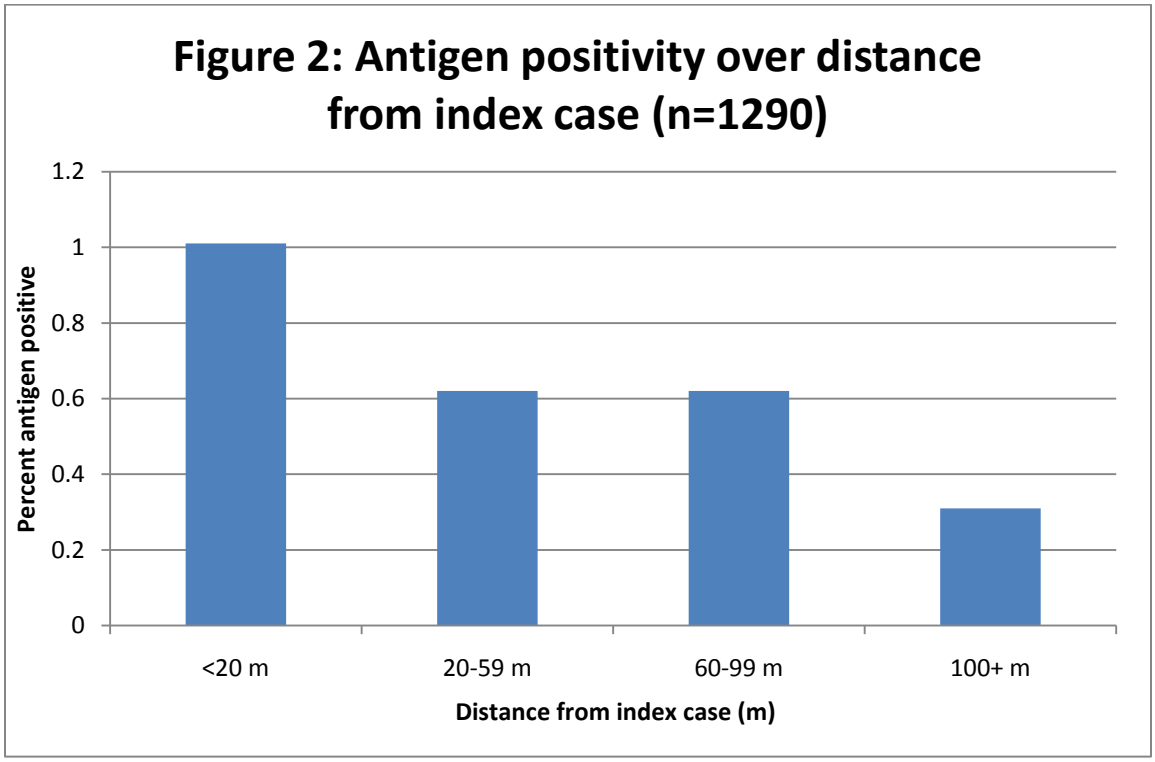
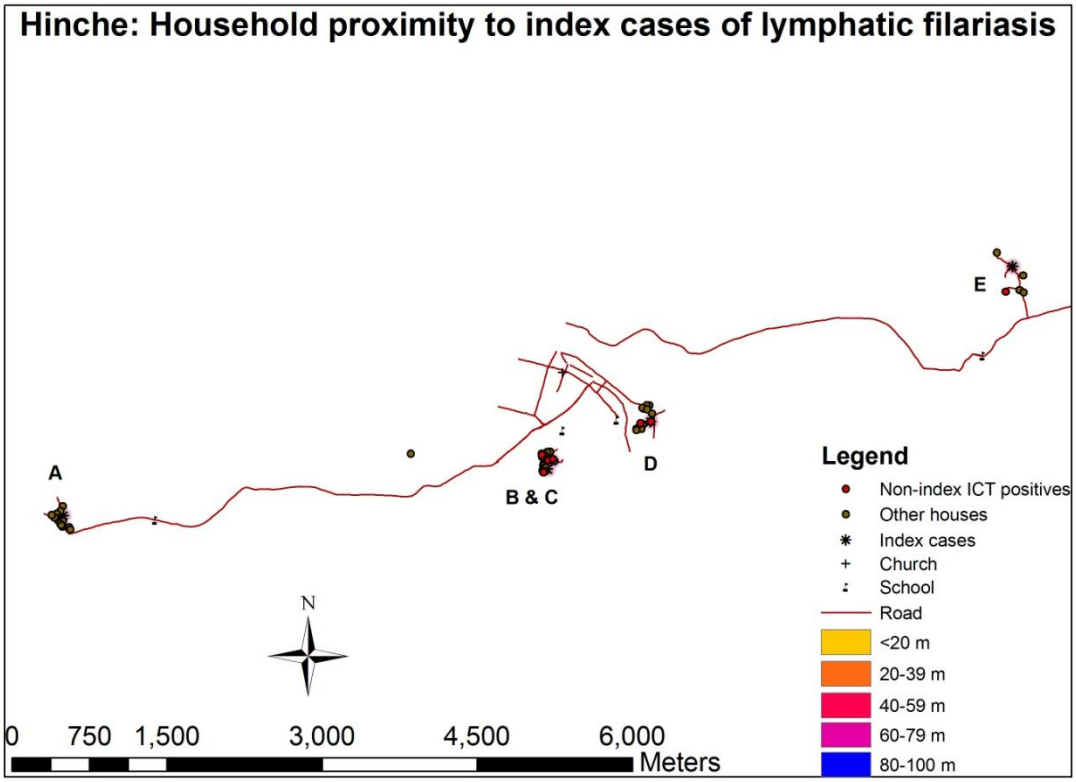


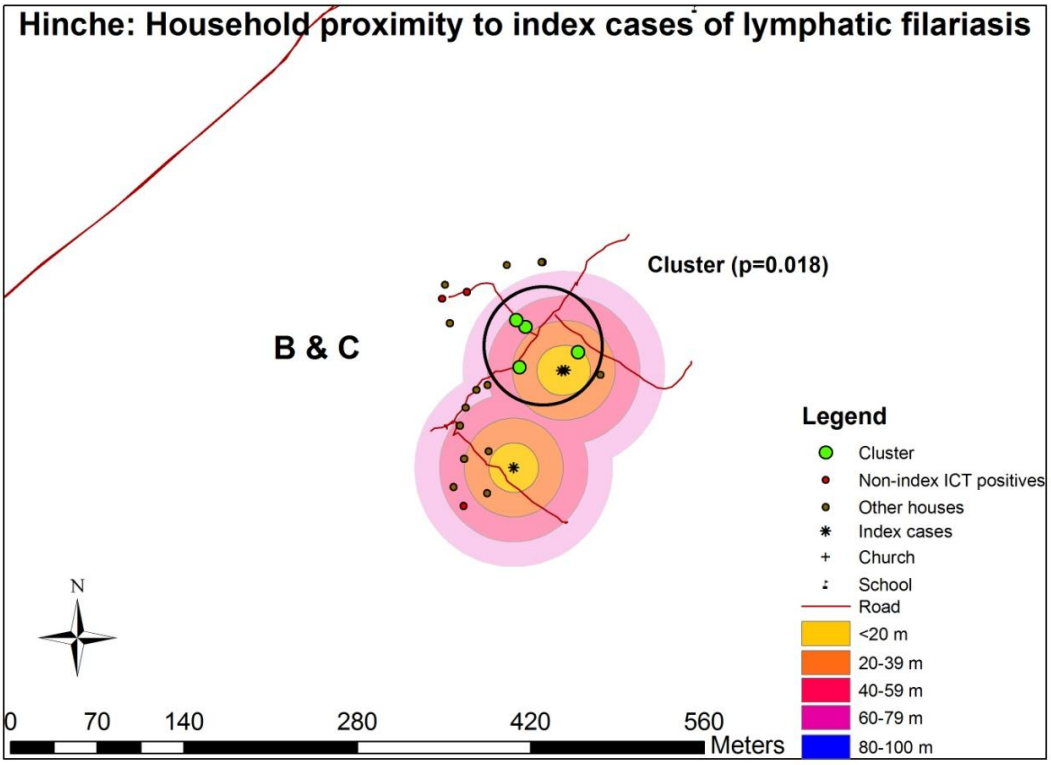
Figure 2: Antigen positivity over distance from index case (n=1290)
Percent antigen positive
0
0.2
0.4
0.6
0.8
1
1.2
<20 m
20-59 m
60-99 m
100+ m
Distance from index case (m)

Figure 3a-c. Maps of Hinche showing clusters of households around index cases

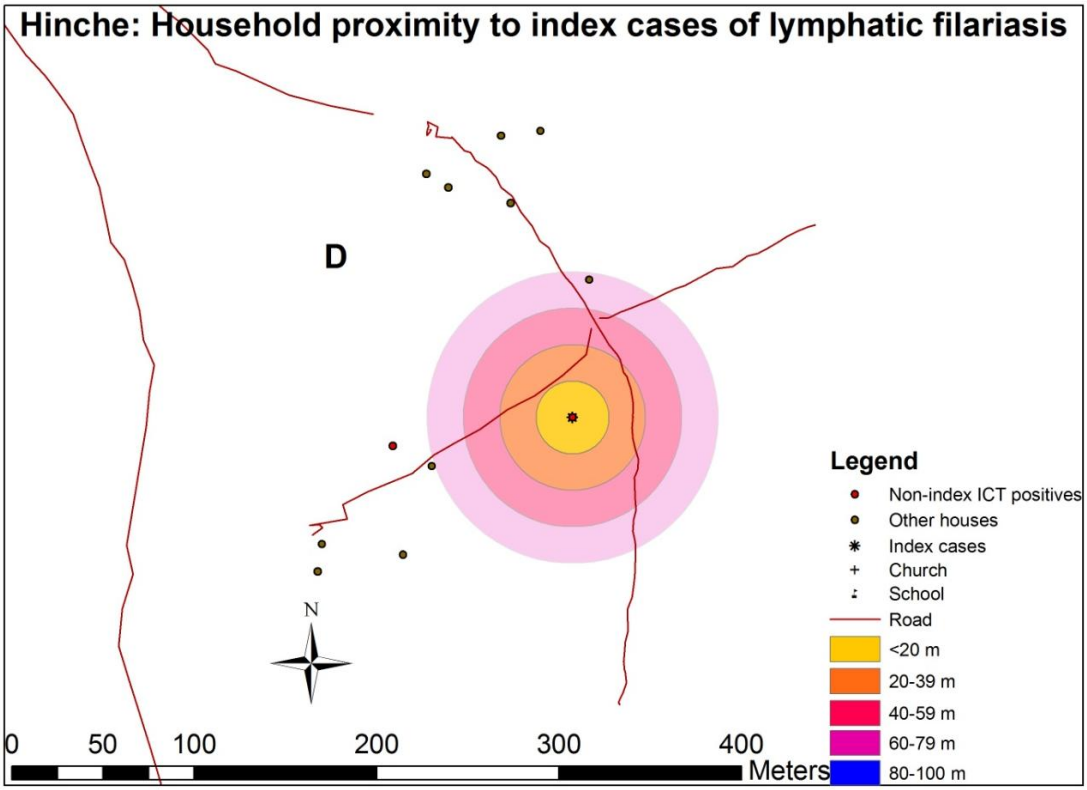
a.



b.


Hinche: Household proximity to index cases of lymphatic filariasis
Cluster (p=0.018)
B & C
Legend
Cluster
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0
70
140
280
420
560
Meters

c.


Hinche: Household proximity to index cases of lymphatic filariasis
D
N
0
50
100
200
300
400
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

Chapter 3: Implications

There has been much controversy about what processes should be employed when nearing stages of elimination. Since smallpox is the only disease in human history to have been globally eradicated there is little to no precedence for the end-stage policies, procedure and methods of surveillance. Thus studies such as this one in low-prevalence areas are particularly important for shaping the end-game plan for diseases like LF that are nearing elimination.

It is important to note that this study has demonstrated that transmission, using antigen prevalence as a proxy, is still occurring in areas that had previously been categorized as areas with low risk of transmission suggesting that areas of low-prevalence may not be equated with areas of low transmission. This may add to the reconsideration of the current 1% cut-off for mass drug administrations. The country-wide mapping techniques in 2001 revealed a prevalence of <1% for all five communes and this study returned prevalence values ranging from 0 to 5.6% in the school survey and 0 to 4.35% in the community survey. There is an obvious disconnect between the national prevalence testing and our community and school evaluations indicating that current national mapping techniques are not sufficiently sensitive for identifying microfoci in the population.

The identified index and AEA cases indicated that transmission occurred at the level of microfoci. Considering one individual to be a potential risk to the persons in close proximity may change the way we approach the treatment of isolated cases. We might employ a ring technique similar to that used in the eradication of smallpox where once a case is detected everyone within close

proximity to a case was treated via prophylaxis to better reduce the chances of transmission to a naïve host. Vector control programs can also be targeted at the area surrounding a case to achieve similar results. Since our analysis revealed that residing within 20 meters of an index or AEA case significantly increased the likelihood of antigen positivity, evaluation and treatment of close contacts should take place within at least 40 meters of a confirmed case.

This study focused on the use of a convenience sample of children being used to identify potential microfoci. While these are smaller subsets of the population being tested they may better capture accurate prevalence values than the currently used technique. The current mapping technique recommended by WHO, RAGFIL, uses a sampling grid of 50x50 km and samples 50 adult males for the presence of hydroceles and antigen presence using ICTs. This study may demonstrate that evaluation prevalence using a convenience sample of children is not only easier to implement, but may also return better, more accurate results. Even if these results are higher than actual prevalence, one could argue that when working to eliminate a disease one would want to utilize a method that would be more sensitive rather than specific. The evaluation of the schoolchildren would do just that. Furthermore, utilizing schoolchildren as indicators of the prevalence within the general population is a better demonstration of newly acquired infections, i.e., recent transmission.

Since there appears to be a continued reservoir of infection even after prevalence drops below 1%, surveillance should be increased in order to monitor

present levels of antigen positivity. Ramaiah et al. reported residual microfilaria prevalence ranging from 0.03 to 0.43% in the population when tested annually over a period of 20 years post MDA (11). It is financially and logistically unrealistic to require a surveillance period of 20 years post MDAs, however increasing the period of surveillance from five years to ten years might be necessary to ensure that transmission has indeed stopped or at least slowed to a point which cannot sustain the filarial lifecycle. The techniques for surveillance when evaluating for the elimination of a disease might be better assessed using the prevalence of antigenemia among schoolchildren, as was suggested for the mapping techniques for LF. In order to ensure the interruption of transmission a higher level of sensitivity must be maintained; thus new tools are likely required. Such demonstrations of the need for increased surveillance and extended periods of treatment are concepts which can be broadly applied to any elimination program. Campaigns to combat LF should be aimed at high levels of coverage during MDAs, which will include addressing any situations of systematic non-compliance, and should emphasize a multi-faceted approach to the prevention of LF, strategies of which should include not only pharmacologic interventions, but also bednet distribution, vector control and continued education in order to make greater strides to eliminate this debilitating disease.

Chapter 4: Expanded Analysis

Narrative:

The logistic model used in the analysis of this study included the following variables:

Outcome:

- ICT status [ICT]- dichotomous variable coded as either positive or negative.

Exposure:

- Distance from index or AEA case [distance]- a categorical variable coded as <20 m, 20-59 m, 60-99 m, and ≥100 m for index analysis and <20 m, 20-59 m, and ≥60 m for AEA analysis. The initial cut off was determined by a sensitivity analysis of dichotomized distances. Upon crude evaluation of several distances 20 m was the most statistically significant level, see Table 2 in the manuscript.

Potential confounders and effect modifiers:

- Age [age]- dichotomized for <15 years and ≥15 years of age. The age cutoff was decided based off of the desire to capture the risk associated with school-age children.
- Gender [gender]-self reported gender was included as sex had been shown to be a potential confounder in the exposure disease relationship in previous studies.
- Commune [commune]-data were collected from five communes in Haiti: Grand Goâve, Hinche, Moron, St. Louis de Sud and Thomazeau. Each

commune is environmentally diverse and exists in different areas of Haiti. The data collected from the commune of Moron did not reveal any ICT-positive results, so it was excluded from analysis for index case analysis and Moron and St Louis de Sud were excluded for the AEA case analysis.

- Locale [locale]-categorized as urban or rural. Since people who live in urban areas are often in close proximity to one another it is sensible to think that a vector-borne disease could be affected by differences in locale. This variable was assessed in crude analyses, but due to the lack of heterogeneity among the population on this variable, it was not used in the regression.

Full interaction model:

$$\text{Logit}[ICT]=\alpha + \beta(\text{distance}) + \gamma_1(\text{age}) + \gamma_2(\text{gender}) + \gamma_3(\text{commune}) + \delta_1(\text{distance*age}) + \delta_2(\text{distance*gender}) + \delta_3(\text{distance*commune}) + \delta_4(\text{distance*age*gender}) + \delta_5(\text{distance*age*commune}) + \delta_6(\text{distance*gender*commune}) + \delta_7(\text{distance*age*gender*commune})$$

Collinearity was assessed on the full interaction model using the 2009 update to the collinearity macro (21). Condition indices (CIs)>30 and Variance Decomposition Proportions (VDPs) >0.5 were used as the criteria for pronounced collinearity. Items were dropped in the following order and collinearity matrices for each step can be seen in Tables 1-5.

Order of dropped variables:

- 4-way interaction

- 3-way interactions
- Distance-gender interaction
- Distance-commune interaction

Even though the collinearity assessment did not indicate collinearity to be present with the 3-level interaction terms the 3 all three 3-level interaction terms were dropped next because had the two 2-level interaction terms that did show collinearity been dropped all three 3-level interaction terms would also have to be dropped for the model to remain hierarchically well-formulated.

The model after assessing for collinearity:

$\text{Logit}[ICT]=\alpha + \beta(\text{distance}) + \gamma_1(\text{age}) + \gamma_2(\text{gender}) + \gamma_3(\text{commune}) + \delta_1(\text{distance*age})$

Assessment of influential observations was performed utilizing Cook's distance and leverage statistics. However, the observations identified in these analyses were not used due to the desire to maintain power.

Interaction assessment:

An interaction assessment was performed on the no collinearity model to assess if age modifies the effect of distance on ICT status. Using the log likelihood techniques it was determined that interaction is not present in the model (see Tables 6-14).

No-interaction gold standard model:

$$\text{Logit}[ICT]=\alpha + \beta(\text{distance}) + \gamma_1(\text{age}) + \gamma_2(\text{gender}) + \gamma_3(\text{commune})$$

Confounding assessment:

In order to address confounding under all possible subsets we applied the 10 % guideline which suggests that should an odds ratio in the confounding assessment be more than 10% from the odds ratio from the full model, confounding is present. Since the exposure of interest is distance we required that it remain in the model. Distance is a 4-level (3-level) categorical variable, so we assessed the change in odds ratios with all possible comparisons, see Table 15. None of the subsetted models showed evidence of confounding based on the 10% guideline so we looked to see if there were significant gains in precision using a different model and even though some models presented a slightly narrower confidence interval, none were significant enough to outweigh controlling for age, gender, and commune. Therefore the full no-interaction models were utilized as the final model for this study.

Tables:

Tables 1-5. Assessment of collinearity

Table 1: Collinearity diagnostics for nonlinear models using the information matrix: Eigenvalues, Condition Indexes, and Variance Decomposition Proportions (VDPs) for the full interaction model

VARIABLE	VDP1	VDP2	VDP3	VDP4	VDP5	VDP6	VDP7	VDP8	VDP9	VDP10	VDP11	VDP12	VDP13	VDP14	VDP15	VDP16
EIGENVAL	8.00E-04	1.80E-03	9.00E-03	1.53E-02	2.05E-02	4.77E-02	1.30E-01	1.70E-01	4.37E-01	6.00E-01	7.93E-01	9.79E-01	1.09E+00	1.55E+00	2.58E+00	7.57E+00
CONDINDX	9.81E+01	6.41E+01	2.90E+01	2.22E+01	1.92E+01	1.26E+01	7.64E+00	6.67E+00	4.16E+00	3.55E+00	3.09E+00	2.78E+00	2.63E+00	2.21E+00	1.71E+00	1.00E+00
Intercept	9.28E-01	5.66E-02	1.41E-02	1.00E-03	1.00E-04	2.00E-04	1.10E-04	2.00E-05	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	1.00E-05	2.00E-05	2.00E-05
dist31	9.28E-01	4.24E-02	4.80E-03	5.10E-03	0.00E+00	8.00E-04	8.32E-03	5.78E-03	6.50E-04	1.00E-05	9.00E-05	8.10E-04	1.79E-03	1.11E-03	1.60E-04	2.00E-05
dist32	9.02E-01	4.10E-02	2.00E-04	1.00E-04	0.00E+00	2.80E-03	1.08E-02	2.24E-02	2.14E-03	0.00E+00	4.52E-03	5.48E-03	7.83E-03	7.30E-04	1.40E-04	9.00E-05
dist33	7.59E-01	2.99E-02	2.00E-04	2.00E-03	8.00E-04	1.90E-03	2.51E-02	7.34E-02	6.77E-02	1.14E-03	2.69E-02	2.06E-03	1.40E-04	8.90E-03	9.00E-05	5.50E-04
age_dich20	4.34E-02	1.00E-03	3.65E-02	1.23E-01	1.40E-01	5.77E-01	6.03E-02	9.19E-03	2.78E-03	1.42E-03	3.00E-04	1.20E-04	6.00E-05	1.80E-04	5.17E-03	3.80E-04
gender	1.99E-01	1.02E-01	2.58E-02	3.30E-01	9.95E-02	2.80E-03	2.24E-03	4.81E-02	1.91E-02	6.36E-02	6.36E-03	4.00E-05	1.20E-03	5.40E-04	1.00E-05	7.10E-04
comm_num41	1.95E-01	4.11E-02	4.43E-01	2.27E-01	3.70E-03	3.74E-02	2.22E-02	1.18E-02	2.97E-03	2.70E-04	7.21E-03	0.00E+00	5.50E-04	7.00E-03	8.80E-04	1.20E-04
comm_num42	2.04E-01	9.03E-02	3.25E-01	2.62E-01	5.00E-04	1.82E-02	3.42E-02	6.40E-04	5.01E-03	1.38E-02	2.87E-02	1.42E-02	0.00E+00	1.92E-03	7.80E-04	3.40E-04
comm_num43	1.04E-01	5.62E-02	1.58E-01	1.52E-01	0.00E+00	1.02E-02	6.21E-02	7.40E-03	4.17E-02	5.16E-02	7.94E-03	1.96E-01	1.51E-01	2.80E-04	5.80E-04	4.60E-04
dist_age	1.72E-01	6.50E-01	1.00E-04	1.19E-02	1.64E-01	3.00E-04	2.00E-05	5.60E-04	1.30E-04	4.00E-05	0.00E+00	1.00E-05	0.00E+00	1.00E-04	3.40E-04	7.00E-05
dist_gen	6.93E-01	9.70E-03	1.89E-01	7.73E-02	1.43E-02	1.01E-02	1.65E-03	3.24E-03	2.80E-04	1.11E-03	1.70E-04	0.00E+00	1.40E-04	2.00E-05	1.00E-04	1.00E-04
dist_comm	7.28E-01	3.00E-04	4.32E-02	2.20E-01	2.70E-03	4.00E-04	1.67E-03	8.20E-04	1.69E-03	4.90E-04	3.00E-05	7.00E-05	0.00E+00	3.20E-04	0.00E+00	1.00E-04
dist_age_gen	1.45E-01	7.81E-01	0.00E+00	0.00E+00	6.20E-03	5.32E-02	6.75E-03	5.49E-03	5.20E-04	1.48E-03	0.00E+00	4.00E-05	2.00E-05	3.20E-04	3.50E-04	9.00E-05
dist_age_comm	2.00E-01	7.79E-01	3.40E-03	1.00E-04	3.60E-03	4.20E-03	6.19E-03	3.25E-03	2.00E-04	2.10E-04	0.00E+00	0.00E+00	1.00E-05	0.00E+00	2.70E-04	4.00E-05
dist_gen_comm	3.81E-01	1.79E-02	5.34E-01	3.98E-02	0.00E+00	1.19E-02	8.58E-03	2.10E-04	4.73E-03	2.00E-04	1.60E-04	1.30E-04	2.00E-05	4.80E-04	3.00E-05	1.60E-04
dist_age_gen_comm	1.59E-01	7.25E-01	1.39E-02	1.00E-04	9.39E-02	3.40E-03	2.16E-03	2.20E-03	1.30E-04	0.00E+00	0.00E+00	0.00E+00	0.00E+00	2.00E-05	3.30E-04	6.00E-05

Table 2: Collinearity diagnostics for nonlinear models using the information matrix: Eigenvalues, Condition Indexes, and Variance Decomposition Proportions (VDPs) dropping the 4 level interaction term

VARIABLE	VDP1	VDP2	VDP3	VDP4	VDP5	VDP6	VDP7	VDP8	VDP9	VDP10	VDP11	VDP12	VDP13	VDP14	VDP15
EIGENVAL	0.0009	0.0095	0.0137	0.0172	0.0457	0.1186	0.1562	0.4314	0.6194	0.7924	0.9814	1.0815	1.4413	2.1981	7.0927
CONDINDX	88.4288	27.3349	22.7493	20.3041	12.4562	7.7332	6.7389	4.0549	3.3839	2.9918	2.6883	2.5610	2.2183	1.7963	1.0000
Intercept	0.9845	0.0133	0.0008	0.0008	0.0004	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
dist31	0.9698	0.0047	0.0039	0.0009	0.0016	0.0023	0.0118	0.0007	0.0000	0.0001	0.0008	0.0016	0.0013	0.0003	0.0000
dist32	0.9387	0.0000	0.0001	0.0008	0.0035	0.0023	0.0316	0.0029	0.0000	0.0044	0.0056	0.0093	0.0005	0.0003	0.0001
dist33	0.7738	0.0001	0.0000	0.0058	0.0026	0.0055	0.0955	0.0754	0.0022	0.0243	0.0023	0.0009	0.0109	0.0001	0.0007
age_dich20	0.0495	0.0014	0.2088	0.0076	0.6560	0.0657	0.0004	0.0021	0.0003	0.0002	0.0001	0.0000	0.0012	0.0060	0.0005
gender1	0.3905	0.0031	0.0341	0.4268	0.0040	0.0149	0.0329	0.0142	0.0740	0.0035	0.0000	0.0009	0.0003	0.0000	0.0008
comm_num41	0.1768	0.5563	0.1382	0.0531	0.0215	0.0046	0.0294	0.0040	0.0000	0.0077	0.0000	0.0007	0.0054	0.0023	0.0001
comm_num42	0.2238	0.4349	0.1549	0.0803	0.0083	0.0235	0.0095	0.0056	0.0078	0.0335	0.0154	0.0000	0.0019	0.0001	0.0005
comm_num43	0.1309	0.2113	0.0895	0.0431	0.0026	0.0293	0.0351	0.0445	0.0431	0.0182	0.1947	0.1571	0.0001	0.0000	0.0006
dist_age	0.0208	0.0040	0.7056	0.2618	0.0004	0.0021	0.0020	0.0005	0.0000	0.0000	0.0001	0.0000	0.0010	0.0016	0.0002
dist_gen	0.6942	0.2200	0.0081	0.0533	0.0166	0.0002	0.0055	0.0003	0.0013	0.0001	0.0000	0.0001	0.0001	0.0001	0.0001
dist_comm	0.6836	0.0191	0.1178	0.1731	0.0002	0.0020	0.0001	0.0027	0.0007	0.0001	0.0001	0.0000	0.0004	0.0000	0.0001
dist_age_gen	0.0015	0.0005	0.2904	0.2350	0.3660	0.0846	0.0065	0.0009	0.0069	0.0000	0.0003	0.0002	0.0034	0.0034	0.0006
dist_age_comm	0.0246	0.0181	0.3713	0.2699	0.0124	0.2589	0.0320	0.0030	0.0016	0.0007	0.0000	0.0000	0.0011	0.0059	0.0006
dist_gen_comm	0.2875	0.5854	0.0633	0.0348	0.0134	0.0078	0.0005	0.0059	0.0003	0.0001	0.0001	0.0000	0.0006	0.0000	0.0002

Table 3: Collinearity diagnostics for nonlinear models using the information matrix: Eigenvalues, Condition Indexes, and Variance Decomposition Proportions (VDPs) dropping the 3-level interaction terms

VARIABLE	VDP1	VDP2	VDP3	VDP4	VDP5	VDP6	VDP7	VDP8	VDP9	VDP10	VDP11	VDP12
EIGENVAL	0.0015	0.0126	0.0446	0.1544	0.3522	0.5429	0.7468	0.9684	0.9885	1.0746	1.5594	5.5542
CONDINDX	59.8783	20.9844	11.1654	5.9979	3.9713	3.1985	2.7272	2.3948	2.3704	2.2735	1.8873	1.0000
Intercept	0.9989	0.0000	0.0008	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001
dist31	0.9433	0.0185	0.0011	0.0277	0.0011	0.0002	0.0004	0.0001	0.0035	0.0012	0.0029	0.0001
dist32	0.8994	0.0000	0.0014	0.0586	0.0055	0.0004	0.0034	0.0056	0.0103	0.0144	0.0006	0.0004
dist33	0.6438	0.0061	0.0001	0.1541	0.1195	0.0011	0.0412	0.0099	0.0005	0.0078	0.0143	0.0017
age_dich20	0.0860	0.0316	0.8451	0.0081	0.0012	0.0006	0.0021	0.0065	0.0125	0.0033	0.0015	0.0015
gender1	0.3755	0.4615	0.0311	0.0064	0.0034	0.1162	0.0011	0.0003	0.0022	0.0004	0.0005	0.0015
comm_num41	0.4348	0.4690	0.0214	0.0467	0.0087	0.0000	0.0096	0.0000	0.0000	0.0007	0.0086	0.0004
comm_num42	0.4210	0.4686	0.0071	0.0232	0.0196	0.0074	0.0376	0.0055	0.0061	0.0008	0.0023	0.0009
comm_num43	0.2106	0.2345	0.0034	0.0568	0.0711	0.0044	0.0181	0.2408	0.0042	0.1550	0.0000	0.0011
dist_age	0.0870	0.0275	0.7906	0.0036	0.0021	0.0065	0.0125	0.0194	0.0333	0.0130	0.0031	0.0014
dist_gen	0.4179	0.5140	0.0494	0.0110	0.0017	0.0047	0.0002	0.0000	0.0004	0.0000	0.0001	0.0005
dist_comm	0.4867	0.4763	0.0129	0.0011	0.0203	0.0003	0.0002	0.0000	0.0004	0.0001	0.0011	0.0004

Table 4: Collinearity diagnostics for nonlinear models using the information matrix: Eigenvalues, Condition Indexes, and Variance Decomposition Proportions (VDPs) dropping the distance-gender interaction term

VARIABLE	VDP1	VDP2	VDP3	VDP4	VDP5	VDP6	VDP7	VDP8	VDP9	VDP10	VDP11
EIGENVAL	0.0024	0.0368	0.1363	0.3324	0.4737	0.7599	0.9683	1.0014	1.0688	1.5128	4.7071
CONDINDX	44.0845	11.3092	5.8772	3.7633	3.1522	2.4888	2.2048	2.1680	2.0986	1.7640	1.0000
Intercept	0.9952	0.0042	0.0001	0.0001	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002
dist31	0.8967	0.0040	0.0789	0.0033	0.0013	0.0003	0.0000	0.0074	0.0024	0.0052	0.0005
dist32	0.8358	0.0000	0.1012	0.0058	0.0022	0.0058	0.0033	0.0243	0.0200	0.0009	0.0008
dist33	0.5684	0.0011	0.1903	0.1373	0.0006	0.0537	0.0131	0.0003	0.0077	0.0249	0.0026
age_dich20	0.0616	0.8669	0.0377	0.0033	0.0002	0.0019	0.0112	0.0097	0.0049	0.0007	0.0021
gender1	0.0008	0.0112	0.0070	0.0584	0.8723	0.0126	0.0059	0.0142	0.0036	0.0006	0.0134
comm_num41	0.8087	0.1077	0.0562	0.0072	0.0012	0.0102	0.0001	0.0001	0.0003	0.0077	0.0006
comm_num42	0.8164	0.0732	0.0319	0.0173	0.0132	0.0310	0.0039	0.0081	0.0011	0.0028	0.0011
comm_num43	0.4133	0.0369	0.0548	0.0709	0.0130	0.0190	0.2247	0.0162	0.1485	0.0012	0.0015
dist_age	0.0625	0.8134	0.0225	0.0054	0.0114	0.0156	0.0274	0.0170	0.0184	0.0044	0.0020
dist_comm	0.8904	0.0821	0.0002	0.0242	0.0002	0.0002	0.0000	0.0006	0.0001	0.0015	0.0005

Table 5: Collinearity diagnostics for nonlinear models using the information matrix: Eigenvalues, Condition Indexes, and Variance Decomposition Proportions (VDPs) dropping the distance-commune interaction term

VARIABLE	VDP1	VDP2	VDP3	VDP4	VDP5	VDP6	VDP7	VDP8	VDP9	VDP10
EIGENVAL	0.0150	0.1228	0.1746	0.4669	0.7868	0.9181	0.9787	1.0939	1.2901	4.1531
CONDINDX	16.6214	5.8152	4.8770	2.9825	2.2975	2.1268	2.0600	1.9485	1.7942	1.0000
Intercept	0.9869	0.0062	0.0045	0.0012	0.0000	0.0000	0.0000	0.0000	0.0000	0.0012
dist31	0.6159	0.1013	0.1913	0.0071	0.0023	0.0380	0.0011	0.0239	0.0157	0.0034
dist32	0.4156	0.2676	0.1154	0.0071	0.0243	0.0583	0.0119	0.0901	0.0059	0.0039
dist33	0.2574	0.4020	0.0982	0.0010	0.1161	0.0136	0.0486	0.0028	0.0556	0.0047
age_dich20	0.7586	0.2085	0.0001	0.0006	0.0018	0.0048	0.0210	0.0001	0.0020	0.0026
gender1	0.0179	0.0002	0.0135	0.9211	0.0114	0.0034	0.0132	0.0000	0.0015	0.0178
comm_num41	0.0157	0.1075	0.6944	0.0060	0.0880	0.0112	0.0003	0.0145	0.0542	0.0082
comm_num42	0.0777	0.1953	0.4306	0.0563	0.1468	0.0160	0.0054	0.0009	0.0633	0.0077
comm_num43	0.0199	0.0426	0.2363	0.0100	0.0001	0.3064	0.1126	0.2635	0.0056	0.0029
dist_age	0.7190	0.1801	0.0026	0.0131	0.0138	0.0046	0.0471	0.0026	0.0148	0.0024

Tables 6-14. Assessment of interaction

Full interaction model:

Table 6. Model Convergence Status-full model
Convergence criterion (GCONV=1E-8) satisfied.

Table 7. Model Fit Statistics-full model		
Criterion	Intercept Only	Intercept and Covariates
AIC	303.53	298.85
SC	308.61	349.64
-2 Log L	301.531	278.85

Table 8. Analysis of Maximum Likelihood Estimates-full model						
Parameter		DF	Estimate	Standard Error	Wald Chi-	Pr > ChiSq
Intercept		1	-3.78	1.20	9.88	0.0017
dist3	1	1	1.28	0.73	3.02	0.0824
dist3	2	1	0.10	0.69	0.02	0.8863
dist3	3	1	0.47	0.64	0.54	0.4611
age_dich2	0	1	-0.51	0.82	0.38	0.539
gender	1	1	0.13	0.36	0.13	0.7219
comm_num4	1	1	0.61	0.49	1.55	0.2133
comm_num4	2	1	0.81	0.51	2.53	0.1117
comm_num4	3	1	-1.17	0.82	2.02	0.1554
dist_age		1	-0.33	0.35	0.87	0.3518

Table 9. Odds Ratio Estimates-full model			
Effect	Point Estimate	95% Wald Confidence Limits	
dist3 1 vs 4	3.58	0.85	15.09
dist3 2 vs 4	1.10	0.29	4.27
dist3 3 vs 4	1.60	0.46	5.60
age_dich2 0 vs 1	0.60	0.12	3.03
gender 1 vs 2	1.14	0.56	2.32
comm_num4 1 vs 4	1.85	0.70	4.86
comm_num4 2 vs 4	2.24	0.83	6.06
comm_num4 3 vs 4	0.31	0.06	1.56
dist_age	0.72	0.36	1.44

Reduced interaction model:

Table 10. Model Convergence Status-reduced model
Convergence criterion (GCONV=1E-8) satisfied.

Table 11. Model Fit Statistics-reduced model		
Criterion	Intercept Only	Intercept and Covariates
AIC	303.53	297.74
SC	308.61	343.45
-2 Log L	301.531	279.74

Table 12. Analysis of Maximum Likelihood Estimates-reduced model						
Parameter		DF	Estimate	Standard Error	Wald Chi-	Pr > ChiSq
Intercept		1	-4.73	0.70	45.33	<.0001
dist3	1	1	1.69	0.61	7.70	0.0055
dist3	2	1	0.37	0.65	0.33	0.5668
dist3	3	1	0.62	0.63	0.97	0.3258
age_dich2	0	1	0.19	0.37	0.26	0.6105
gender	1	1	0.14	0.36	0.14	0.7074
comm_num4	1	1	0.59	0.49	1.45	0.2291
comm_num4	2	1	0.82	0.51	2.61	0.1062
comm_num4	3	1	-1.15	0.82	1.96	0.1613

Table 13. Odds Ratio Estimates-reduced model			
Effect	Point Estimate	95% Wald Confidence Limits	
dist3 1 vs 4	5.41	1.64	17.83
dist3 2 vs 4	1.45	0.41	5.13
dist3 3 vs 4	1.85	0.54	6.35
age_dich2 0 vs 1	1.21	0.58	2.50
gender 1 vs 2	1.15	0.56	2.34
comm_num4 1 vs 4	1.81	0.69	4.76
comm_num4 2 vs 4	2.27	0.84	6.14
comm_num4 3 vs 4	0.32	0.06	1.58

Table 14. Assessment of Interaction using the log liklihood technique			
reduced	full	diffference	chi square df=1
279.74	278.85	0.89	0.3457

Table 15. Assessment of confounding and estimation of precision

Table 15. Confounding assessment using all possible subsets and being evaluated with the 10% guideline															
	≤20 to 100±						20-59 to 100±					60-99 to 100±			
V's in model	POR	10% GS	lclm	uclm	CI width	POR	10% GS	lclm	uclm	CI width	POR	10% GS	lclm	uclm	CI width
All (GS)	5.41	X	1.64	17.83	16.19	1.45	X	0.41	5.13	4.72	1.85	X	0.54	6.35	5.81
dist, age, gender	5.02	yes	1.61	15.61	14.00	1.53	yes	0.46	5.11	4.66	1.87	yes	0.56	6.27	5.71
dist, age, comm	5.43	yes	1.65	17.89	16.25	1.45	yes	0.41	5.15	4.74	1.85	yes	0.54	6.32	5.78
dist, gender, comm	5.41	yes	1.65	17.76	16.12	1.46	yes	0.41	5.17	4.76	1.88	yes	0.55	6.44	5.89
dist, age	4.99	yes	1.60	15.51	13.91	1.53	yes	0.46	5.13	4.67	1.86	yes	0.55	6.22	5.67
dist, gender	5.05	yes	1.62	15.69	14.07	1.54	yes	0.46	5.16	4.70	1.87	yes	0.56	6.33	5.77
dist, comm	5.40	yes	1.64	17.76	16.12	1.46	yes	0.41	5.18	4.76	1.86	yes	0.55	6.37	5.83
dist	4.99	yes	1.60	15.51	13.90	1.55	yes	0.46	5.18	4.72	1.87	yes	0.56	6.27	5.71

Appendices:

Appendix I: Background and literature review

Figure 1: Life cycle of *W bancrofti* (22)

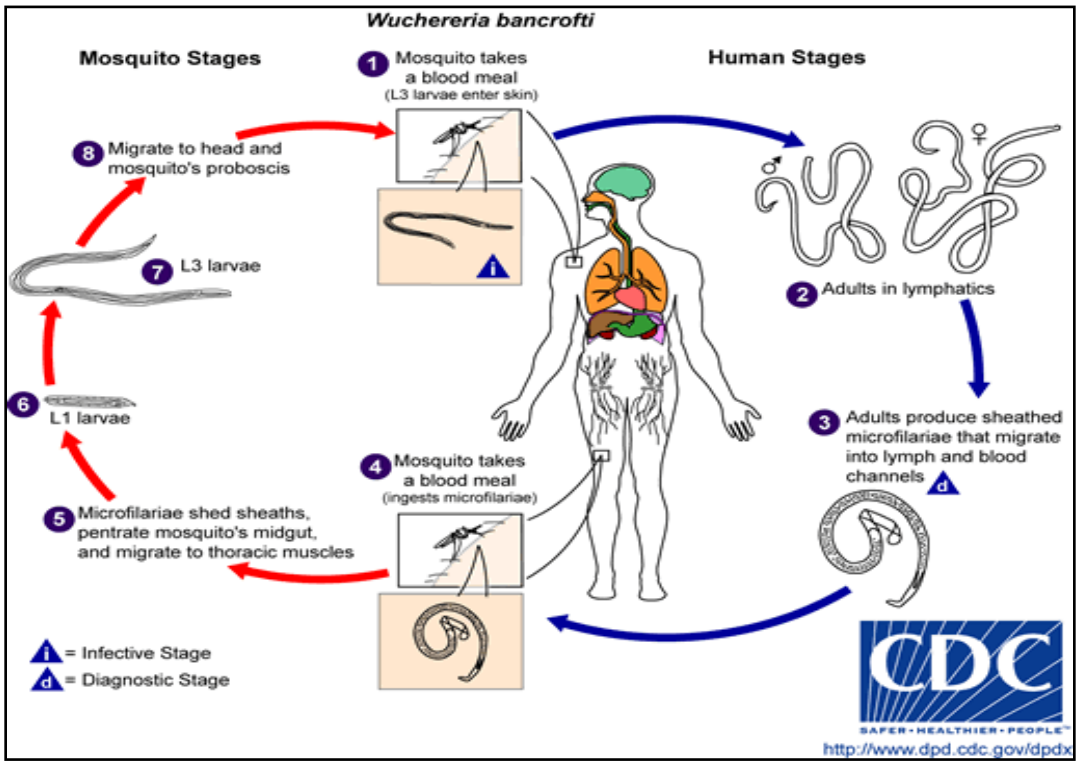


Figure 2: Map of communes in Haiti used for present study

Appendix II: Manuscript

Surveys:

Figure 1: School Survey implemented in Haiti 2001-2003

Filaryoz Lymphatique
Ecole Survey

Komin __________ Ecole __________________

Vil __________ Dat __________________

					Adresse		Ag (+/-)	Ag (+/-)	Ag (+/-)	Ag (+/-)	Ag (+/-)	Ag (+/-)	Ag (+/-)	Mf
No.	Nom	Prenom	Laj	Sexe	SC	LOC	10 min	5hrs(C&M)	5hrs(Sony)	5hrs (C)	24hrs(C&M)			

Figure 2: Survey given to ICT positive children following school survey in Haiti 2001-2003

ID Number : _____

Version 15

L'Hopital Ste Croix / CDC / Inivesite Notre Dame

Konsantman moun yo sou transmisyon Filarioz la, Haiti 2002 / pou antijen + endividi

---

Dat rankont la :_____/_____/2002 Index child: Wi ( ), Non ( )

Non moun nan: _____ Ki fanmi: _____

Komin :_____ Seksyon :_____ Zòn :_____ Vil :_____

Ki kote kay la ye :_____ Nimero kay la :_____

Ki laj li: _____ane

Seks li Gason / Fi (fè yon ti wonn)

Ki metye li:_____

Konbyen moun ki nan kay la :_____

Non manman li:_____ Non papa li:_____

Filarioz se yon maladi ki trè koni an Ayiti, gen kote ki genyen li plis ke kèk lòt. Pou tèt sa li enpòtan pou nou konnen ki kote moun ki gen filarioz yo ap viv. Deplasman moun ki gen filarioz yo kapab change kote yo jwen ki gen enfeksyon filarioz an Ayiti. Moun kap voyaje al nan lòt lokalite kapab enfekte. N'ap essaye etidie a ki etandi moun ki gen filarioz yo kapab transmèt maladi ya nan peyi yo. Avèk enfòmasyon sa yo nou espere devlope yon plan pi elabore sou ki jan nou ka debarase Ayiti de filarioz. Nou ta renmen tou pose ou kèk kesyon sou kay ou e sou sa ou posede, e sou ki jan ou ekspoze a moustik sa va ede nou pi byen konprann eksposisyon ki trè asosye a filarioz.

1. Depi tanto 5 an, pou travay ou o lekòl ou, eske ou te deplase al nan yon lòt kote? Wi ( ), Non ( )
Si non, continue avek kesyon 2

	Komi-n	Seksyon	Zon	Konbyen tan ou te fe la
Si oui, ki kote ou ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa

2. Depi tanto 5 an, eske ou te deplase al nan yon lòt kote pou te visite fanmi avek zanmi ou? Wi ( ), Non ( )
Si non, continue avek kesyon 3

	Komi-n	Seksyon	Zon	Konbyen tan ou te fe la
Si oui, ki kote ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa

ID Number : _____

3. Depi tanto 5 an, eske ou te deplase al nan yon lòt kote pou te visite yon moun ki te malad? Wi ( ), Non ( )
Si non, continue avek kesyon 4

	Komi-n	Seksyon	Zon	Konbyen tan ou te fe la
Si oui, ki kote ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa

4. Depi tanto 5 an, eske ou te deplase al nan yon lòt kote pou yon fèt nasyonal ou yon celebrasyon?
Si non, continue avek kesyon 5 Wi ( ), Non ( )

	Komi-n	Seksyon	Zon	Konbyen tan ou te fe la
Si oui, ki kote ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa

5. Depi tanto 5 an, eske mwen manke yon bagay? Eske pou you rezon kelkonk ou te voyaje nan tan sa yo al nan yon lòt zòn? *Si non, continue avek kesyon 6* Wi ( ), Non ( )

	Komi-n	Seksyon	Zon	Konbyen tan ou te fe la
Si oui, ki kote ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa
Ki lòt kote anko ou te ale?				ane (fè yon ti wonn) mwa

Pou moun kap poze kesyon an:
Mande nenpòt moun bò kote ou, eske yon moun ka sonje ki lè moun sa a te deplase? Epi ranpli enfòmasyon anba sa yo. Eske li fè sans? Eske ou ka suiv tout tan positif ke moun nan fè an deyò vilaj la?

ID Number : _____

6. Eske ou te toujou abite nan kay sa a? *Si wi, continue avek kesyon 16* Wi ( ), Non ( )

	Komi-n	Seksyon	Zon	Konbyen tan ou te fe la
7. Si, NON konbyen tan ou te fe la				ane (fè yon ti wonn) mwa
8. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
9. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
10. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
11. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
12. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
13. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
14. Ki lot kote anko ou te abite?				ane (fè yon ti wonn) mwa
15. Ki laj li gen?: ane Are these numbers equal? Wi ( ), Non ( ) Poukisa?			Total time :	ane

16. Pendan periòd de tan sa-a eske out te viv :

	Cap Aysyen	Carachol	Gonaive	Leogane	Milo	Pordepè	Port au Prince	Seau d'eau	Verretes
Si wi check									

17. Eske ou te lekol? Wi ( ), Non ( )
Si wi nan ki pi gro klas ou te rive? E konbyen ane ou te fe: Klas _____
Ane _____

18. Eske dlo antre kay ou-a? Wi ( ), Non ( )

19. Eske ou gen latrin nan lakou la kay ou-a? Wi ( ), Non ( )
Si wi, ki distans li ye ? ____ an met

20. Eske fanmi ouan posede bagay sa yo ?
Radyo _____, Televizyon _____, Kabrit _____, Konchon _____, Bef _____, Cheval _____, Bisiklet _____,

21. Avek ki sa kay la fet? (fè yon ti wonn)
An blok beton _____ , Pay _____ , Kis + motye _____ , Klis + te _____ , Bwa _____ ,
Bwa + pay _____ , Roch + motye _____ , Fey tol_____, Yon lot bagay _____

22. Konbyen de fwa ou ka pike pa moustik yo? (fè yon ti wonn)
Raman ou jamè / Okazionèlman / souvan

23. Ki lè nan jounen yan ou pike pa plis moustik? (ansèkle yon repons)
Le maten / Nan mitan jounen yan / Pita apre-Midi / Aswè / Nenpòt ki lè / Pa janm pike

Figure 3: Community survey implemented in Haiti 2003

Commune: Grand Goave, Grand Goave | School: Batisseur de L'Espoir | Child: Felix Margarette kid 17 | Rural ( ), Urban (X)

ID: (ggbg100) - M | Dat: 14 March 2002 | Signature:

ID Moun	ID Kay	Nimero kay la	Nom	Prenom	Consent / Assent	laj (lane)	sexe	Eske ou te toujou rete nan vil sa-a?	ICT Results
1								Wi ( ), Non ( )	
2								Wi ( ), Non ( )	
3								Wi ( ), Non ( )	
4								Wi ( ), Non ( )	
5								Wi ( ), Non ( )	
6								Wi ( ), Non ( )	
7								Wi ( ), Non ( )	
8								Wi ( ), Non ( )	
9								Wi ( ), Non ( )	
10								Wi ( ), Non ( )	
11								Wi ( ), Non ( )	
12								Wi ( ), Non ( )	
13								Wi ( ), Non ( )	
14								Wi ( ), Non ( )	
15								Wi ( ), Non ( )	
16								Wi ( ), Non ( )	
17								Wi ( ), Non ( )	
18								Wi ( ), Non ( )	
19								Wi ( ), Non ( )	
20								Wi ( ), Non ( )	
21								Wi ( ), Non ( )	
22								Wi ( ), Non ( )	
23								Wi ( ), Non ( )	
24								Wi ( ), Non ( )	
25								Wi ( ), Non ( )	
26								Wi ( ), Non ( )	
27								Wi ( ), Non ( )	
28								Wi ( ), Non ( )	
29								Wi ( ), Non ( )	
30								Wi ( ), Non ( )	
31								Wi ( ), Non ( )	
32								Wi ( ), Non ( )	
33								Wi ( ), Non ( )	
34								Wi ( ), Non ( )	
35								Wi ( ), Non ( )	
36								Wi ( ), Non ( )	
37								Wi ( ), Non ( )	
38								Wi ( ), Non ( )	

Diagnostic tool analysis for school survey:

Tables 1-5 diagnostic tool evaluations by commune

Summary for Grand Goave School Survey, December 2001, Grand Goave, Haiti

Performance of the Binax Card Test Compared to the Og4C3 ELISA

Og4C3 Result	ICT Positive (%)	ICT Negative (%)			
Positive	14 (87.5%)	2 (12.5%)	16	Sensitivity	58
Negative	10 (10%)	94 (90%)	104	Specificity	98
	24	96	120	PPV	88
				NPV	90

Summary for Hinche School Survey, March 2002, Hinche, Haiti

71 tested

Performance of the Binax Card Test Compared to the Og4C3 ELISA

Og4C3 Result	ICT Positive (%)	ICT Negative (%)			
Positive	11 (92%)	1 (8%)	12	Sensitivity	65
Negative	6 (10%)	53 (90%)	59	Specificity	98
	17	54	71	PPV	92
				NPV	90

Summary for Thomazeau School Survey, March 2002, Thomazeau, Haiti

30 tested

Performance of the Binax Card Test Compared to the Og4C3 ELISA

Og4C3 Result	ICT Positive (%)	ICT Negative (%)			
Positive	5	3	8	Sensitivity	100
Negative	0	22	22	Specificity	88
	5	25	30	PPV	63
				NPV	100

Summary for Moron School Survey, May 2003, Moron, Haiti

7 tested

Performance of the Binax Card Test Compared to the Og4C3 ELISA

Og4C3 Result	ICT Positive (%)	ICT Negative (%)	
Positive	0	0	0
Negative	7	0	7
	7	0	7

Summary for St Louis du Sud School Survey, May 2003, St Louis du Sud, Haiti

5 tested

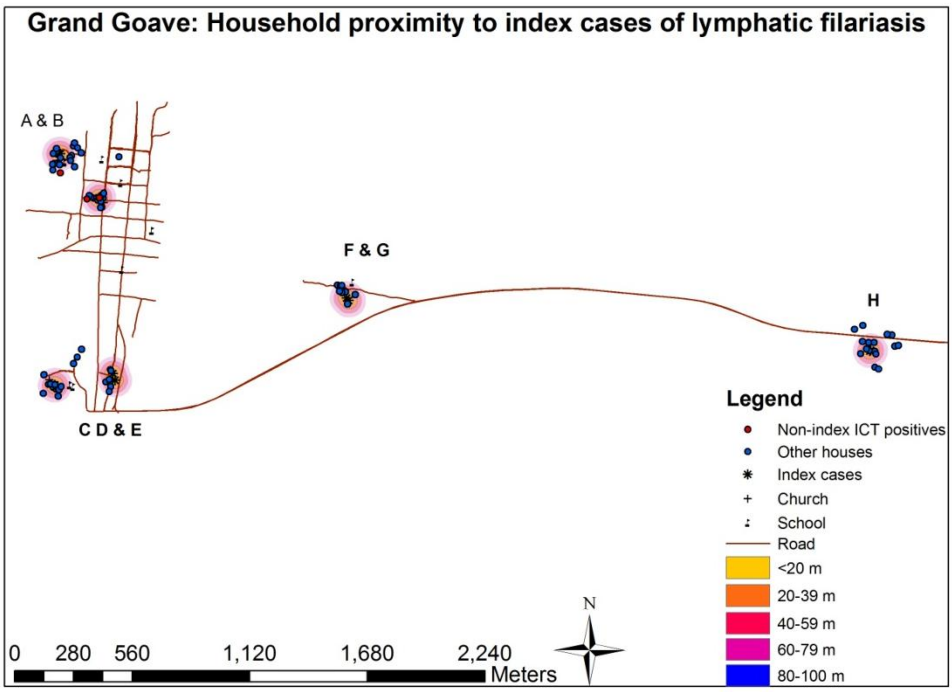
Performance of the Binax Card Test Compared to the Og4C3 ELISA

Og4C3 Result	ICT Positive (%)	ICT Negative (%)	
Positive	3	0	3
Negative	2	0	2
	5	0	5

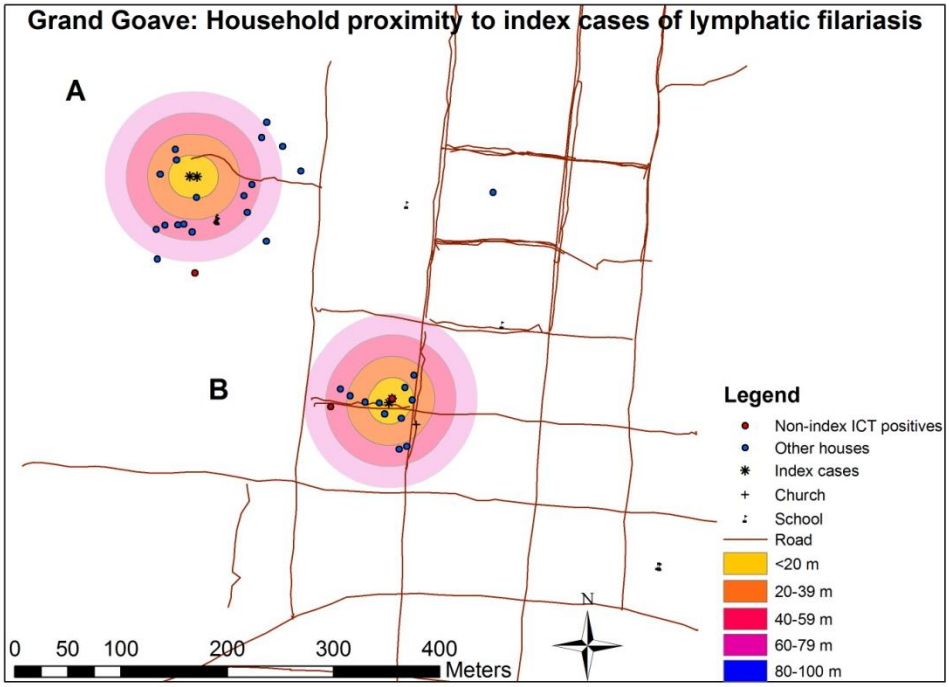
Maps:

Figure 4a-e: Community maps of Grand Goâve showing proximity to index cases

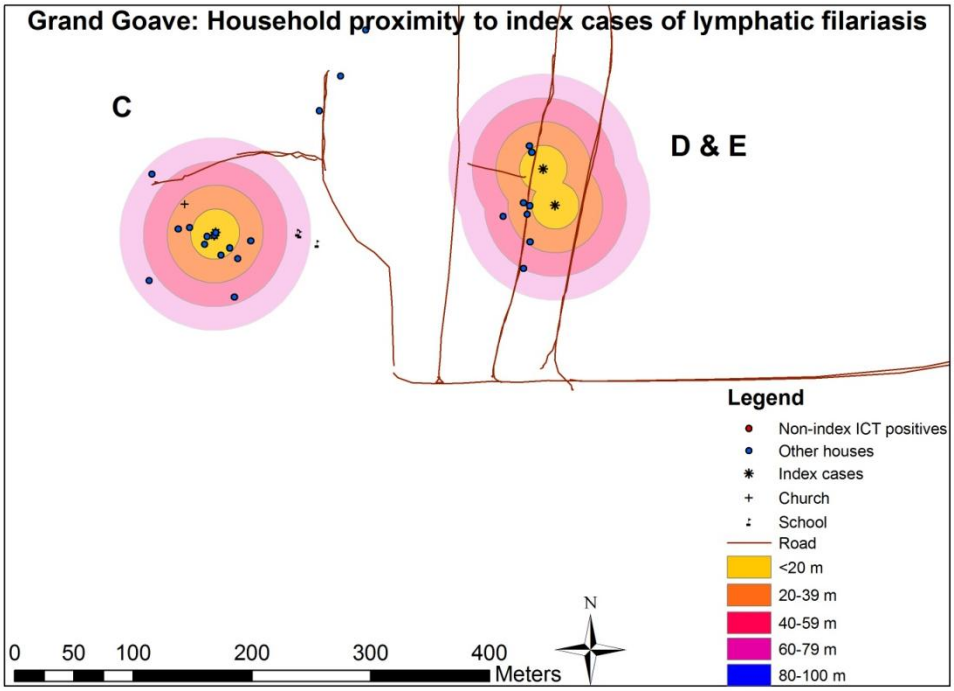
a.



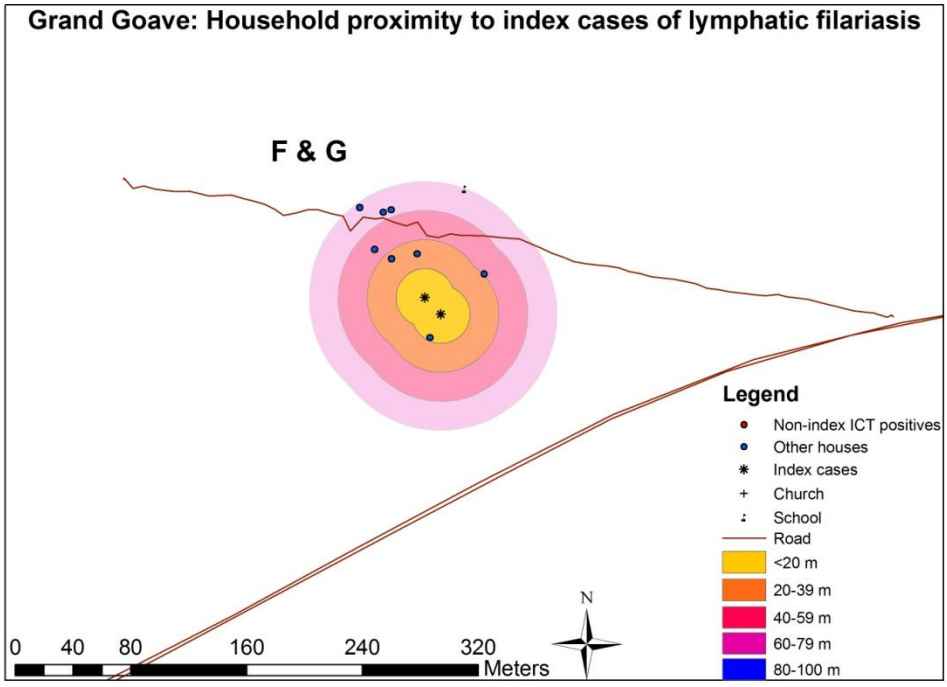
b.


Grand Goave: Household proximity to index cases of lymphatic filariasis
A
B
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 50 100 200 300 400
Meters

c.


Grand Goave: Household proximity to index cases of lymphatic filariasis
C
D & E
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 50 100 200 300 400
Meters

d.


Grand Goave: Household proximity to index cases of lymphatic filariasis
F & G
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 40 80 160 240 320
Meters

e.

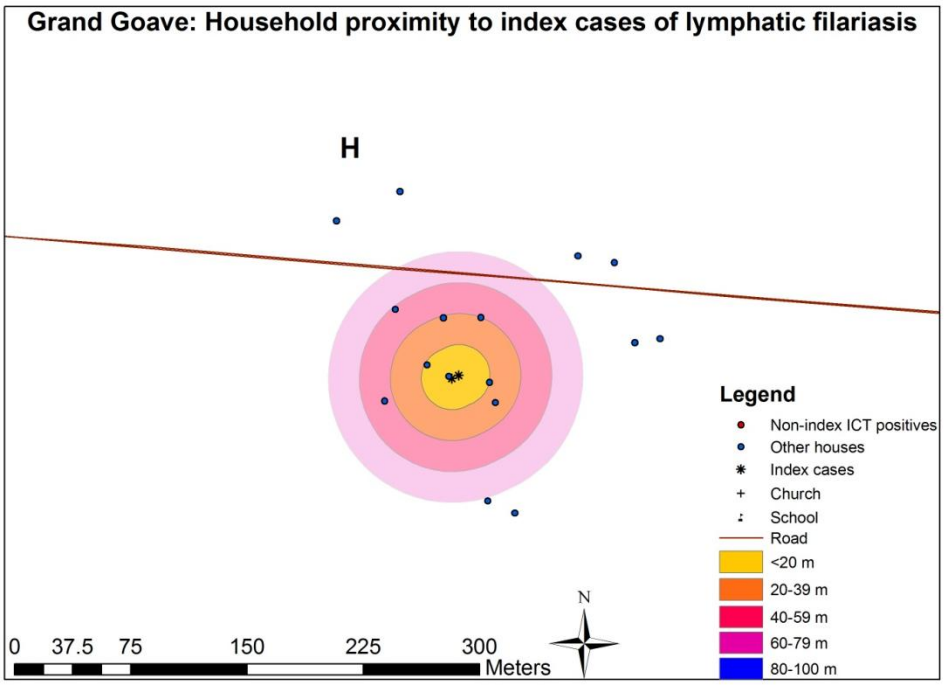
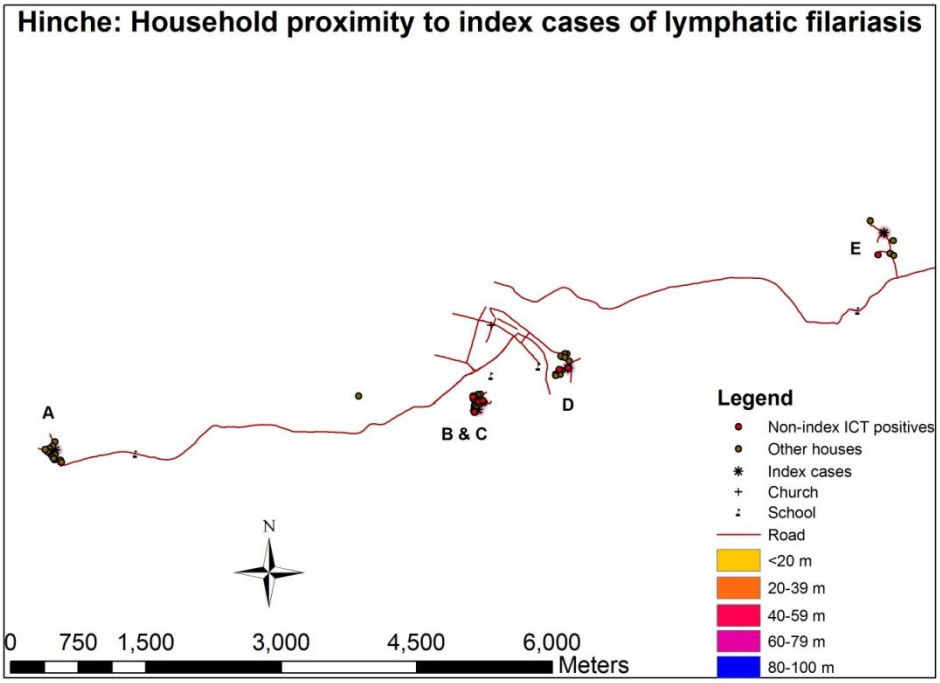
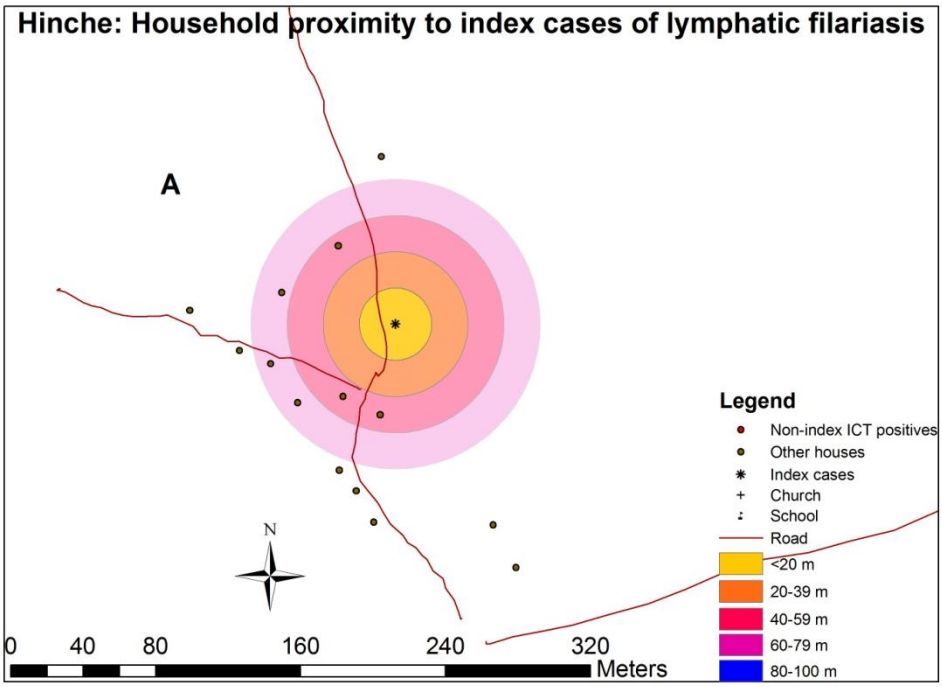

Grand Goave: Household proximity to index cases of lymphatic filariasis
H
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 37.5 75 150 225 300
Meters

Figure 5a-e: Community maps of Hinche showing proximity to index cases

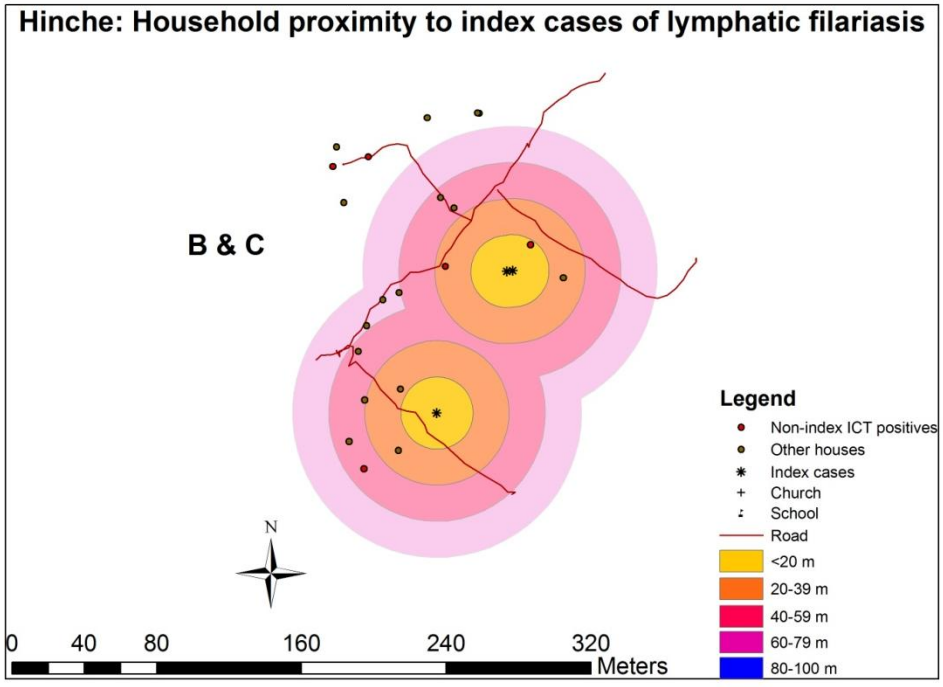
a.



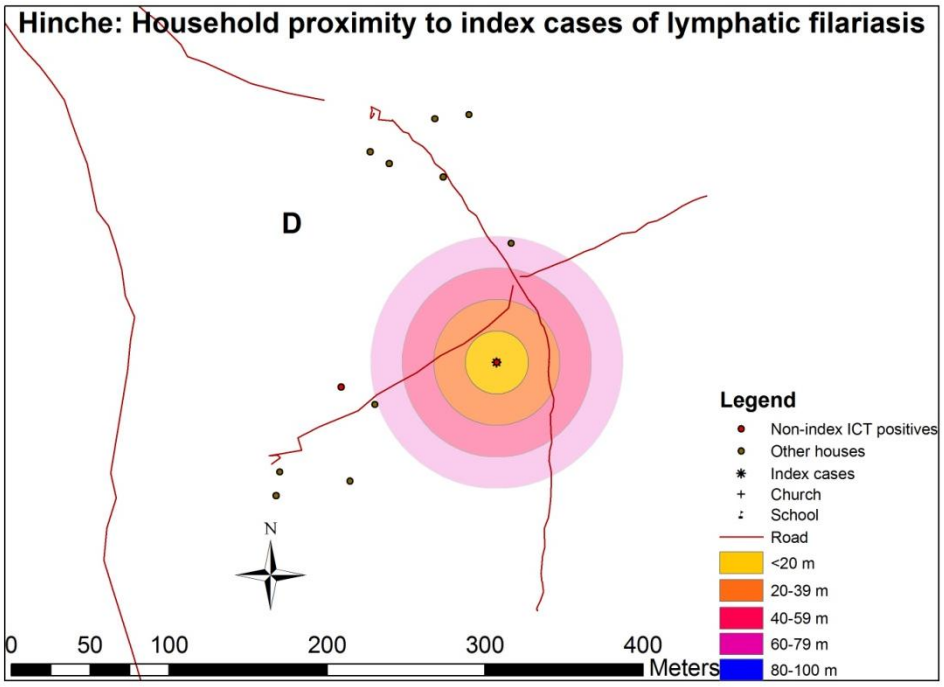
b.


Hinche: Household proximity to index cases of lymphatic filariasis
A
N
0 40 80 160 240 320
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

c.


Hinche: Household proximity to index cases of lymphatic filariasis
B & C
N
0 40 80 160 240 320
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

d.


Hinche: Household proximity to index cases of lymphatic filariasis
D
N
0 50 100 200 300 400
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

e.

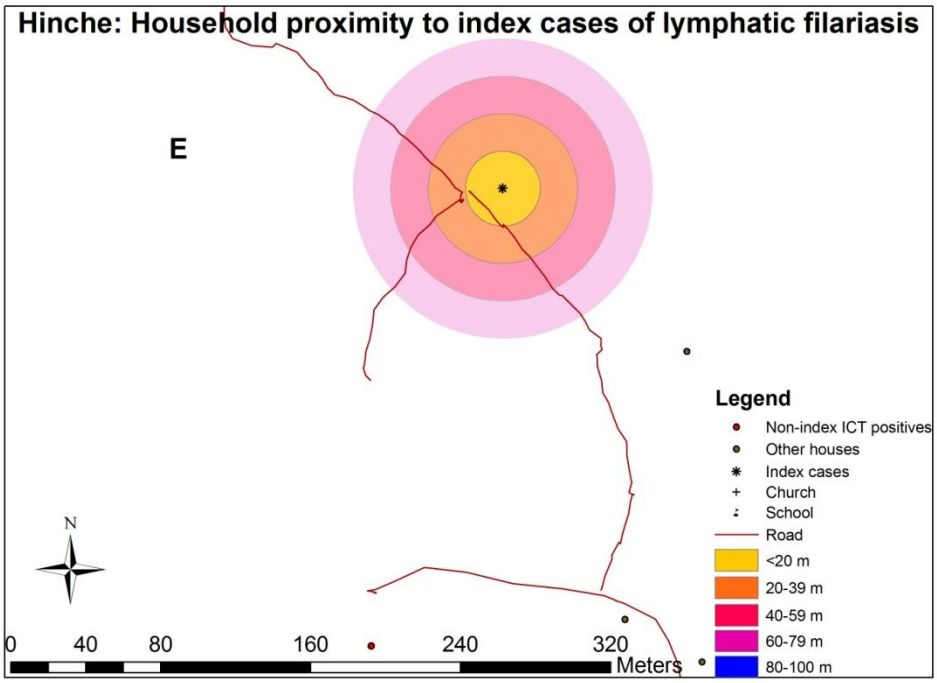
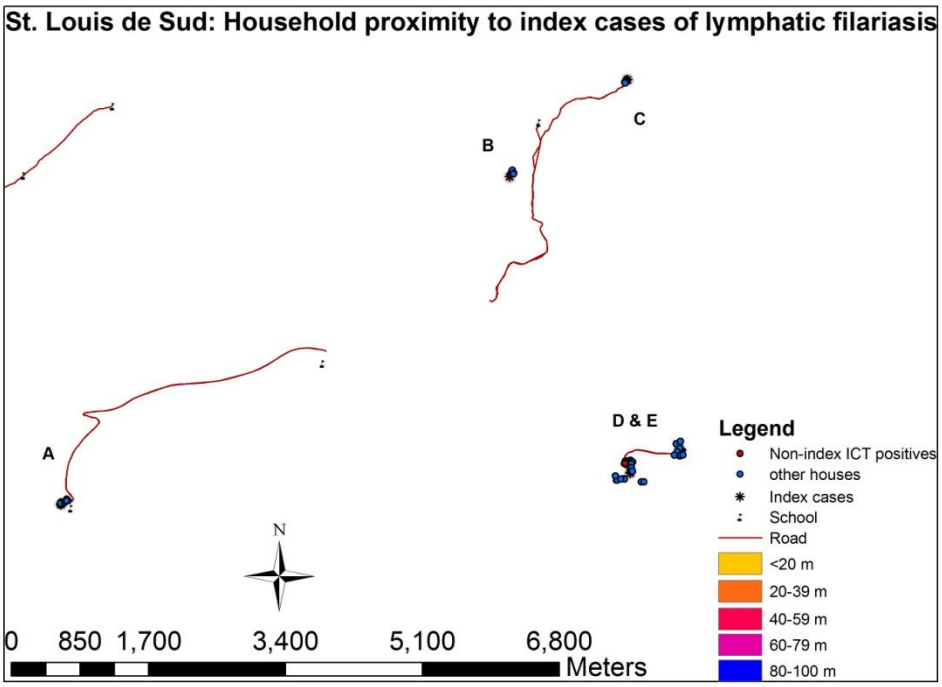
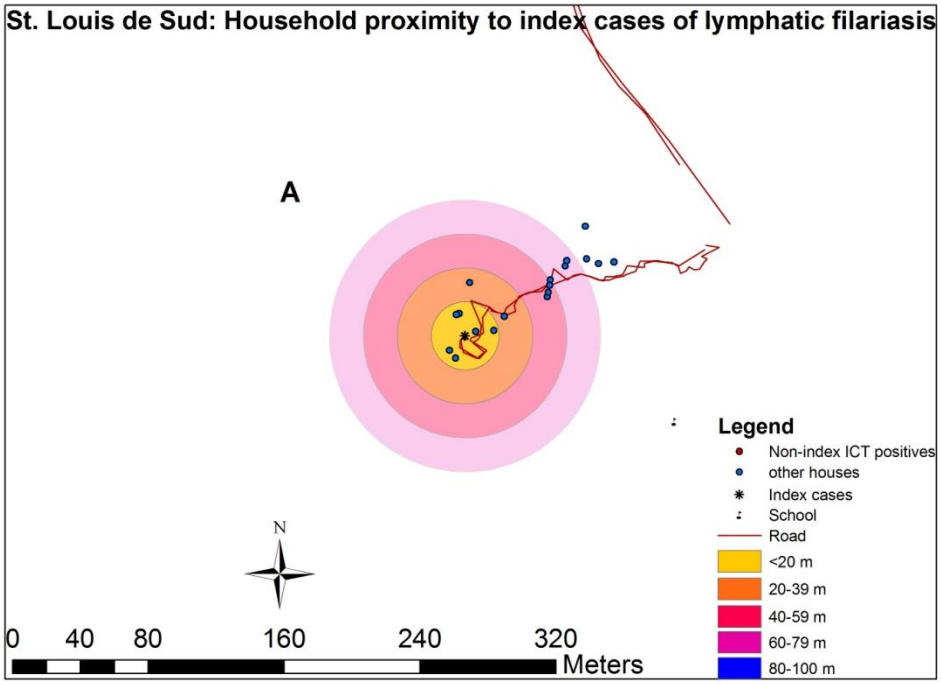

Hinche: Household proximity to index cases of lymphatic filariasis
E
N
0 40 80 160 240 320
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

Figure 6a-d: Community maps of St. Louis de Sud showing proximity to index cases

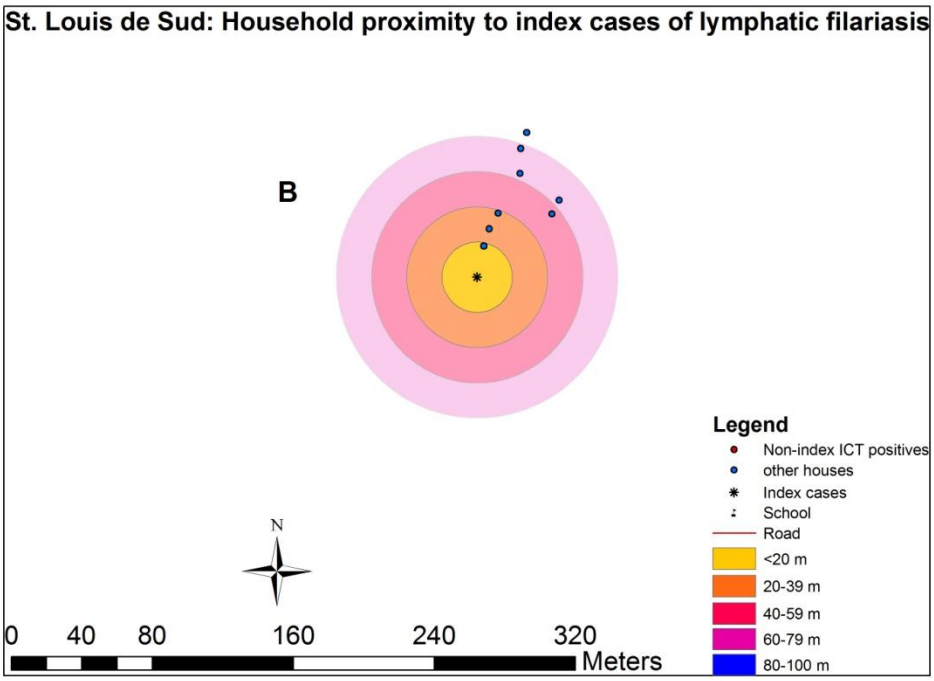
a.



b.


St. Louis de Sud: Household proximity to index cases of lymphatic filariasis
A
N
0 40 80 160 240 320
Meters
Legend
Non-index ICT positives
other houses
Index cases
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

c.


St. Louis de Sud: Household proximity to index cases of lymphatic filariasis
B
N
0 40 80 160 240 320
Meters
Legend
Non-index ICT positives
other houses
Index cases
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

d.

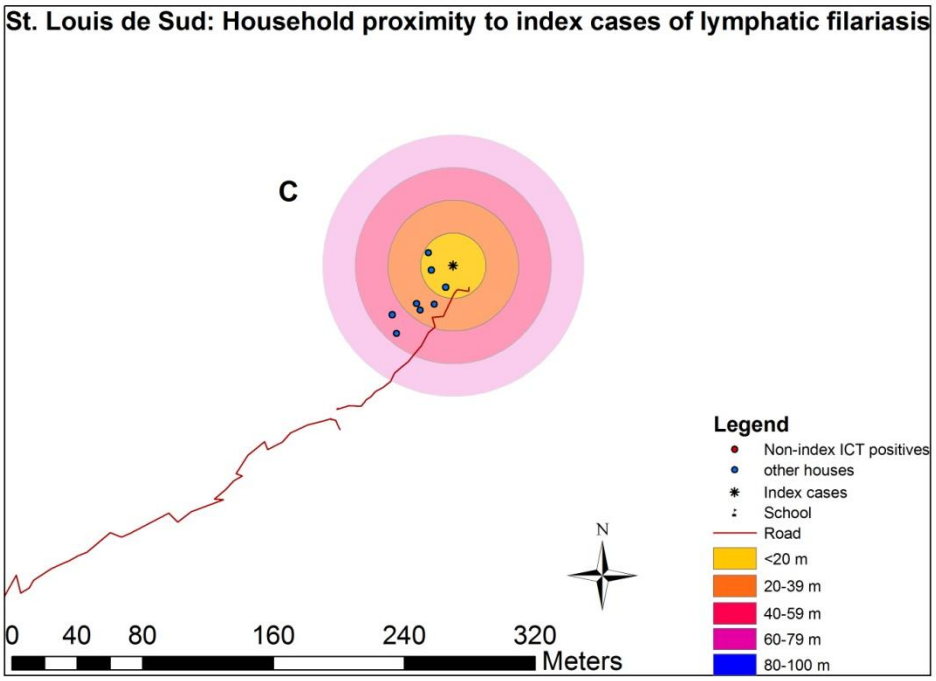
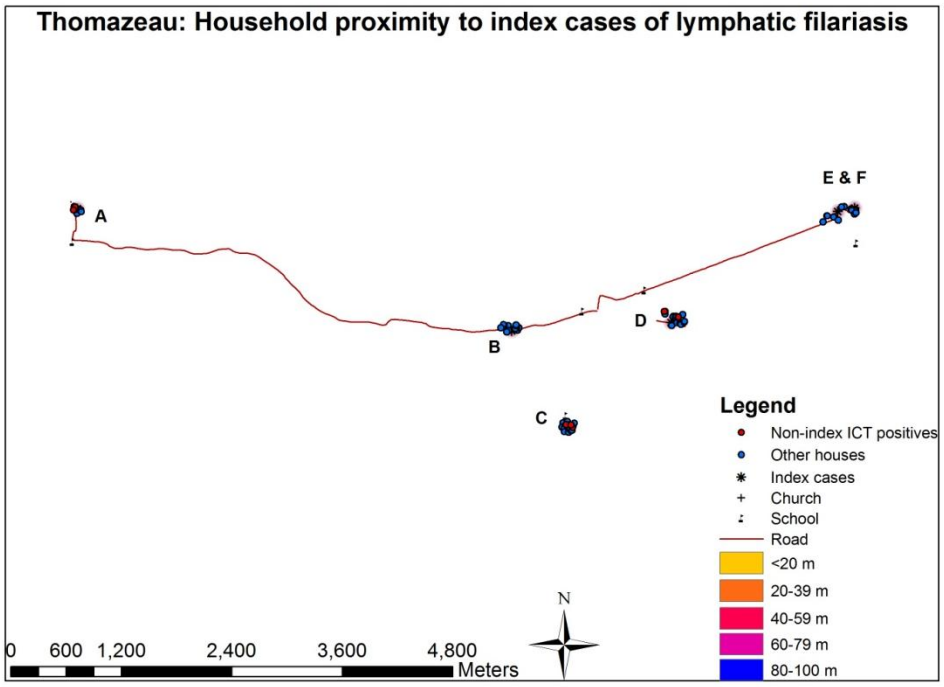
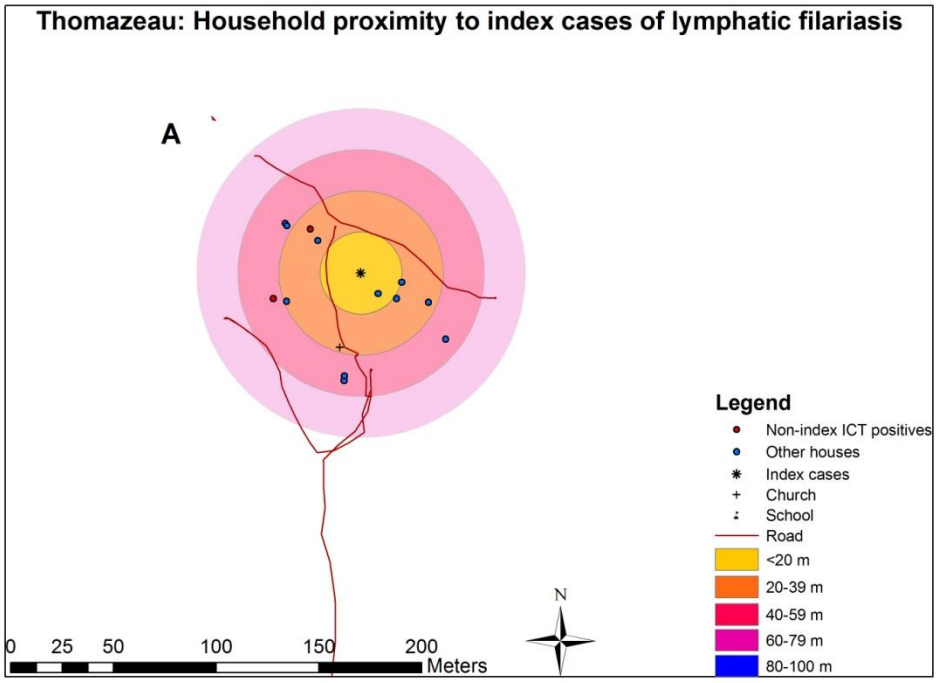

St. Louis de Sud: Household proximity to index cases of lymphatic filariasis
C
N
0
40
80
160
240
320
Meters
Legend
Non-index ICT positives
other houses
Index cases
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

Figure 7a-f: Community maps of Thomazeau showing proximity to index cases

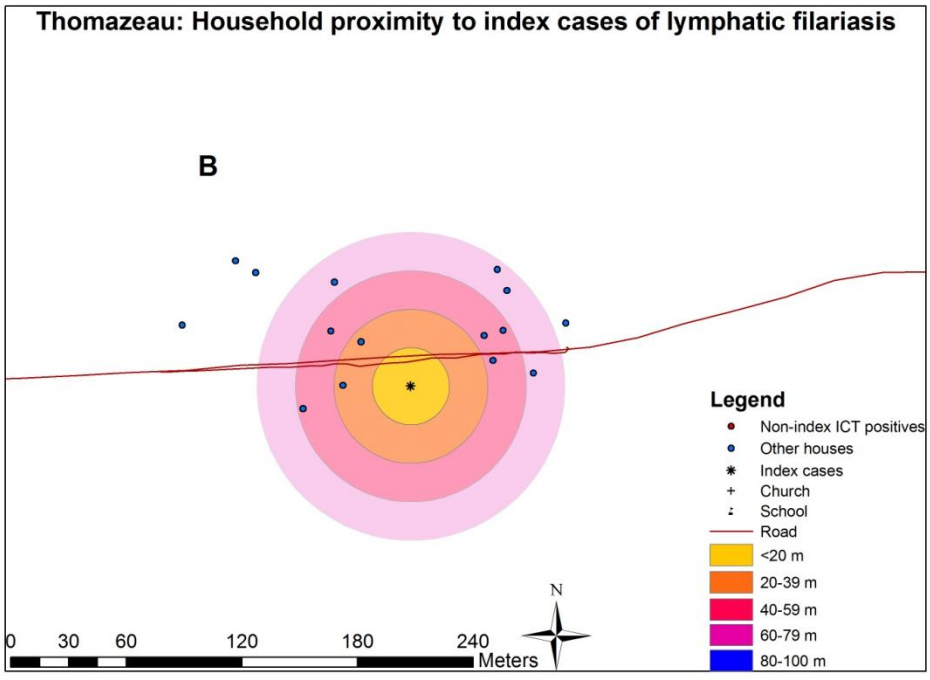
a.



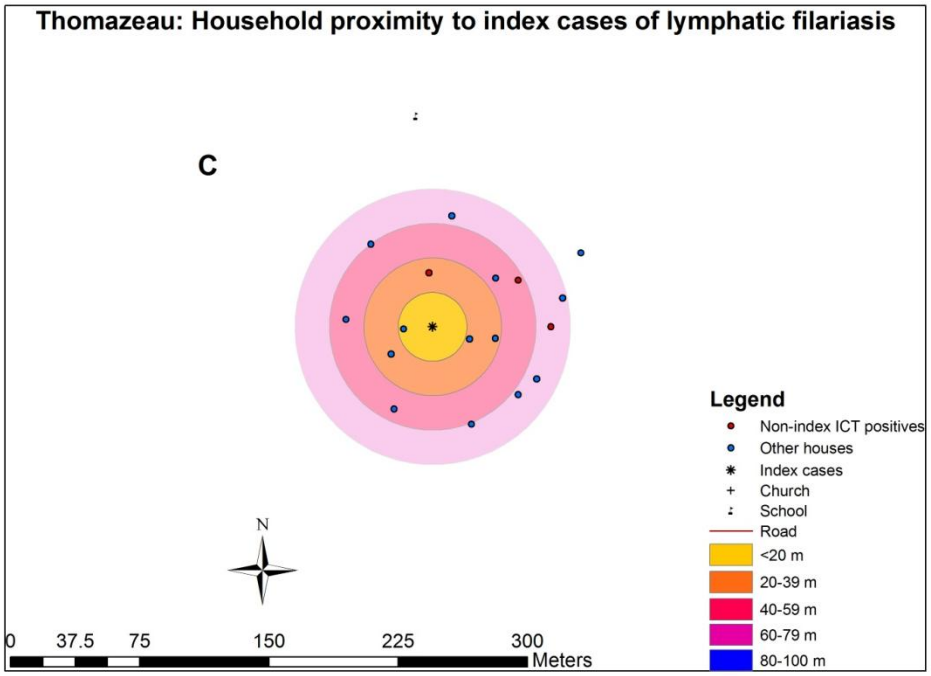
b.


Thomazeau: Household proximity to index cases of lymphatic filariasis
A
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 25 50 100 150 200
Meters

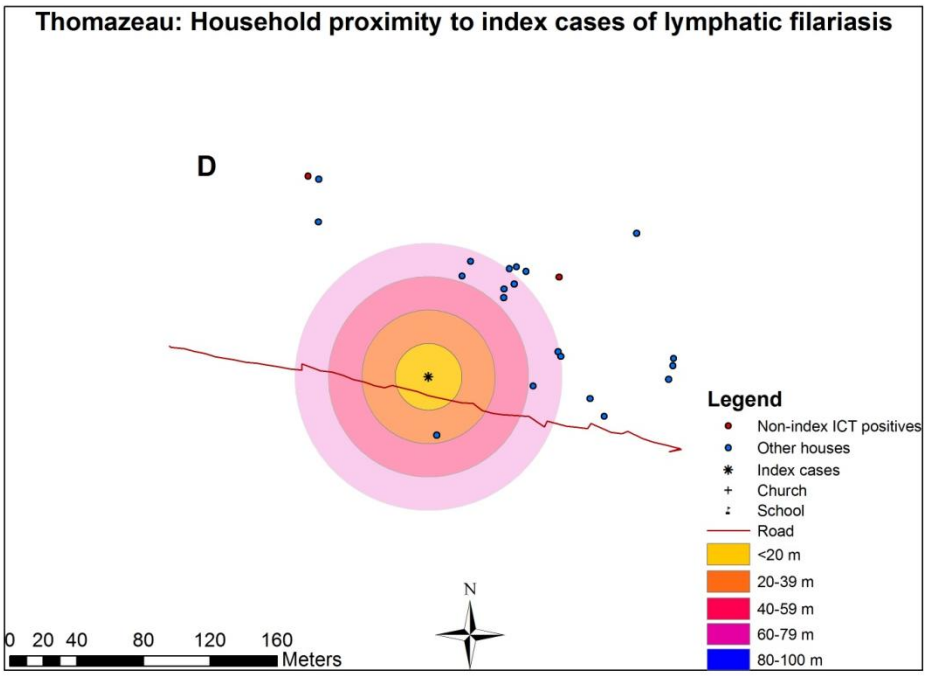
c.


Thomazeau: Household proximity to index cases of lymphatic filariasis
B
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 30 60 120 180 240
Meters

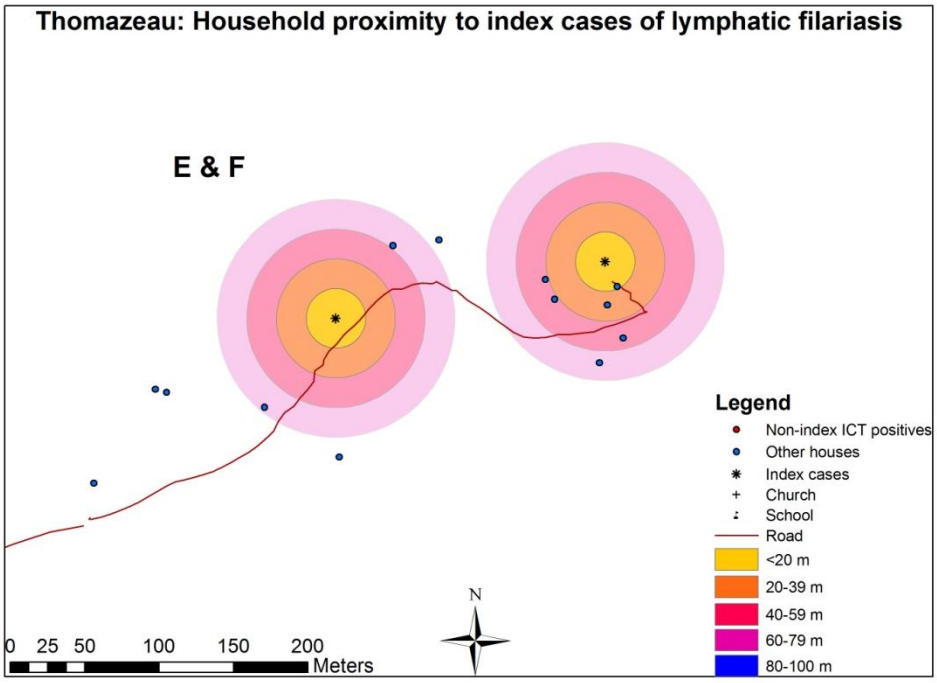
d.


Thomazeau: Household proximity to index cases of lymphatic filariasis
C
N
0 37.5 75 150 225 300
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

e.


Thomazeau: Household proximity to index cases of lymphatic filariasis
D
N
0 20 40 80 120 160
Meters
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m

f.


Thomazeau: Household proximity to index cases of lymphatic filariasis
E & F
Legend
Non-index ICT positives
Other houses
Index cases
Church
School
Road
<20 m
20-39 m
40-59 m
60-79 m
80-100 m
N
0 25 50 100 150 200
Meters

Other figures:

Figure 7: Population density of Haiti by commune (23)

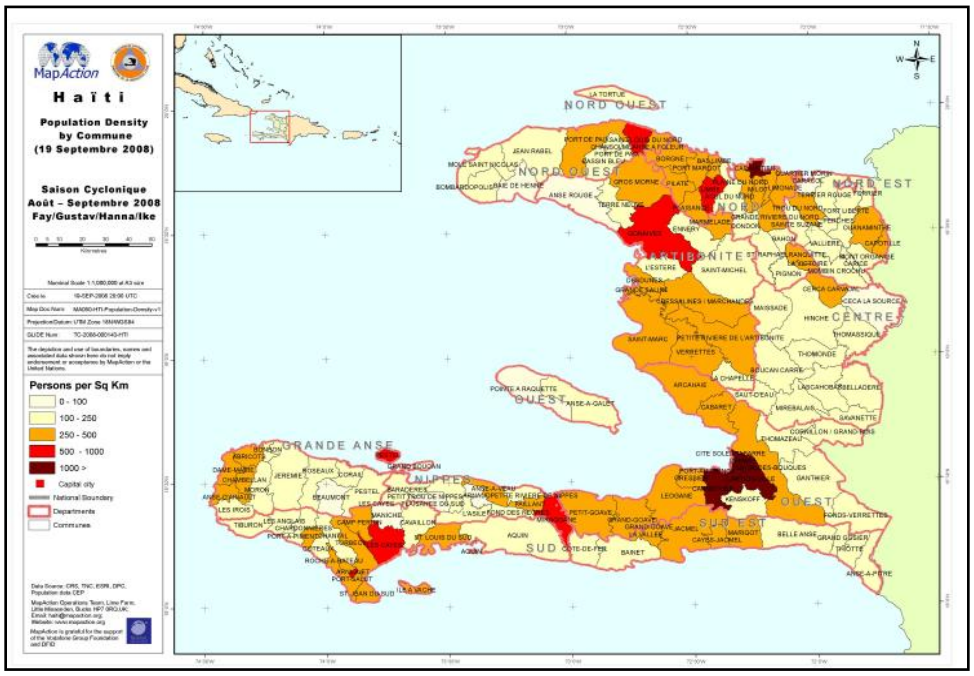
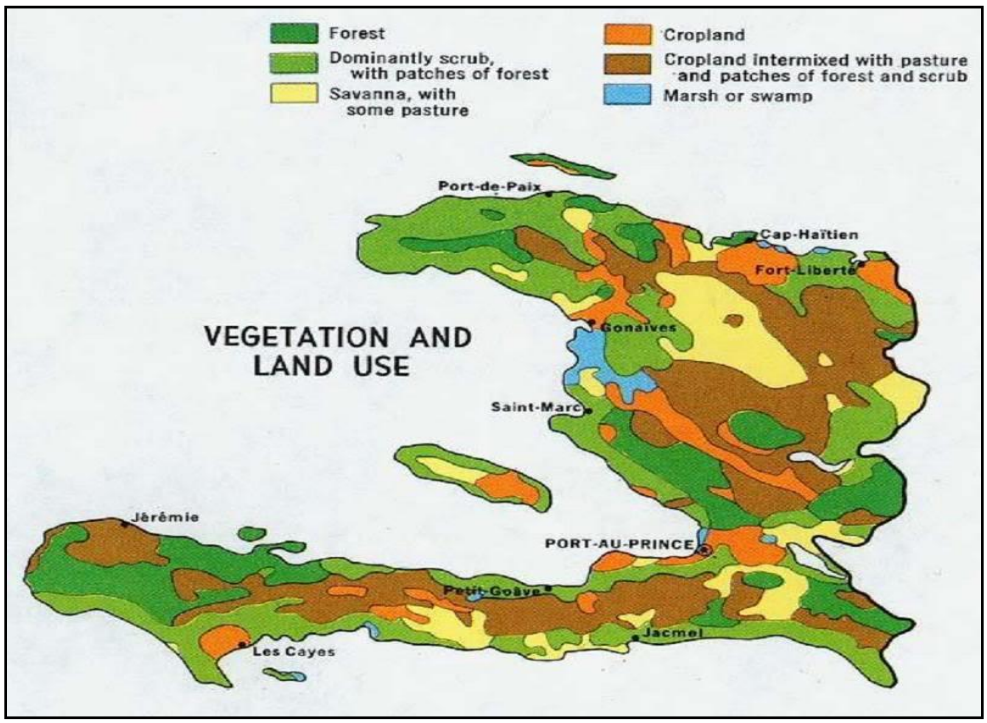


Figure 8: Vegetation and land use in Haiti (24)



Collinearity Macro

```
/*************************************************************************
**********************
Program:    collinearity_macro.sas
Date:       Sometime before 2005
Authors:    Mathew Zack (MZ, original author), Jim Singleton (JS),
            Catherine Satterwhite (CS)
Purpose:    Generate collinearity diagnostics from the variance-
covariance matrix produced in
            nonlinear regression based on output generated from PHREG,
LOGISTIC, or GENMOD.
            Reference:
                DAVIS CE, HYDE JE, BANGDIWALA SI, NELSON JJ. AN EXAMPLE
OF DEPENDENCIES AMONG
                VARIABLES IN A CONDITIONAL LOGISTIC REGRESSION.  IN:
MOOLGAVKAR SH,
                PRENTICE RL, EDS.  MODERN STATISTICAL METHODS IN
CHRONIC DISEASE
                EPIDEMIOLOGY.  NEW YORK:JOHN WILEY & SONS, INC.,
1986:140-7.

Input:      Output (captured in datasets) from PHREG, LOGISTIC, or
GENMOD.  See below
            for instructions.  Macro must be included in code before
calling.
Output:     Collinearity diagnostic matrix (and supporting output)

Change History:
04/26/2005  JS  Modified to handle covariates included in class
statement
                (name of file: collingenmodv9c.sas)
04/21/2009  CS  Increased length of PARNUM in datastep NEXT_1 to $25,
PARM to $25 in
                datastep NEXT_1A, and _NAME_ to $25 in datastep NEXT_4
to increase display
                length of variable name in PROC GENMOD output
                Added code to increase number of parameters that can be
used in PROC GENMOD
                (previously limited to 9, now can have up to 20)--this
becomes important
                when a class variable with multiple levels is used in
the model
                Added additional information to explain macro and
detailed call instructions
*************************************************************************
**********************/

/*************************************************************************
**********************
To use this macro with PROC GENMOD:
    -If the REPEATED statement is not used, add:
        *COVB to the model statement as an option (model x=y/covb)
        *MAKE 'PARMINFO' OUT=<DATASETNAME1>;
        *MAKE 'COV'      OUT=<DATASETNAME2>;
```

```
    -If the REPEATED statement is used (correlated data analysis-
cluster identification), add:
        *COVB to the MODEL statement as an option (model x=y/covb)
        *COVB to the REPEATED statement as an option (repeated/covb)
        *MAKE 'PARMINFO' OUT=<DATASETNAME1>;
        *MAKE 'GEERCOV'  OUT=<DATASETNAME2>;

Macro call:
    %COLLIN(COVDSN=<DATASETNAME2>, PROCDR=GENMOD,
PARMINFO=<DATASETNAME1>)

Example:
%include 'E:\collinearity_macro.sas';
proc genmod data=five;
    class facility_id region;
    model total_positive/total_tests=year prop_15to20 prop_black
prop_naat region
                                     year*prop_15to20 year*prop_black
                                     year*prop_naat/dist=bin link=logit
covb;
    repeated subject=facility_id/type=exch covb;
    make 'PARMINFO'   out=set1;
    make 'GEERCOV'    out=set2;
    title Collinearity assessment, full model;
run;

%collin (covdsn=set2, procdr=genmod, parminfo=set1);
run;
**********************************************************************
**********************/

/**********************************************************************
**********************
To use this macro with PROC LOGISTIC or PROC PHREG:
    -Add:
        *COVOUT to the proc statement as an option (...data=xx covout)
        *OUTEST=<DATASETNAME2> to the proc statement as an option
(...data=xx outest=set2)
        *COVB to the MODEL statement as an option (model x=y/covb)
        *FREQ COUNT;

Macro call (only need to pass first parameter value):
    %COLLIN(COVDSN=<DATASETNAME2>, PROCDR=, PARMINFO=)
    -or-
    %COLLIN(COVDSN=<DATASETNAME2>)

Example:
%include 'E:\collinearity_macro.sas';
proc logistic data=one desc covout outest=set2;
    model brc=smk ses age smk*ses smk*age/covb;
    freq count;
    title Homework 4, Question 2, part i;
run;

%collin (covdsn=set2);
run;
```

```
**************************************************************************
**********************/

/**************************************************************************
**********************
In GENMOD, SAS does not record the variable names in the output
variance-covariance dataset.
The next section of code replaces the parm variable with the actual
names of the variables
and renames parm to _name_ to conform to the output datasets generated
by LOGISTIC and
PHREG.

If there are more than 20 variables in the model statement (including
all class levels if
the class statement is used) SAS will stop processing and the final
collinearity matrix
will not be produced.  To allow more parameters, add corresponding code
lines to data next_1
and data next_1_a within the GENMOD do-loop, which makes GENMOD
covariance output similar
to LOGISTIC and PHREG.  In some output variance-covariance matrices,
there will be a record
for scale; this is deleted in the next_3 datastep.  A dummy record for
ESTIMATE is inserted
in datastep next_4 to simulate output from LOGISTIC and PHREG.
**************************************************************************
**********************/

options mprint symbolgen mlogic;

%macro collin(covdsn=, procdr=, parminfo=);

%if %upcase(&procdr)=GENMOD %then %do;
data next_1;
    set &parminfo;
    attrib parnum format=$25.;
    parnum=parameter;
    if parnum='Prm1' then parnum='Prm01';
    if parnum='Prm2' then parnum='Prm02';
    if parnum='Prm3' then parnum='Prm03';
    if parnum='Prm4' then parnum='Prm04';
    if parnum='Prm5' then parnum='Prm05';
    if parnum='Prm6' then parnum='Prm06';
    if parnum='Prm7' then parnum='Prm07';
    if parnum='Prm8' then parnum='Prm08';
    if parnum='Prm9' then parnum='Prm09';
    if parnum='Prm10' then parnum='Prm10';
    if parnum='Prm11' then parnum='Prm11';
    if parnum='Prm12' then parnum='Prm12';
    if parnum='Prm13' then parnum='Prm13';
    if parnum='Prm14' then parnum='Prm14';
    if parnum='Prm15' then parnum='Prm15';
    if parnum='Prm16' then parnum='Prm16';
    if parnum='Prm17' then parnum='Prm17';
    if parnum='Prm18' then parnum='Prm18';
    if parnum='Prm19' then parnum='Prm19';
```

```
    if parnum='Prm20' then parnum='Prm20';
    rename parnum=parm;
run;

proc sort data=next_1;
    by parm;
run;

data next_1a;
    set &covdsn;
    attrib parm format=$25.;
    parm=rowname;
    if parm='Prm1' then parm='Prm01';
    if parm='Prm2' then parm='Prm02';
    if parm='Prm3' then parm='Prm03';
    if parm='Prm4' then parm='Prm04';
    if parm='Prm5' then parm='Prm05';
    if parm='Prm6' then parm='Prm06';
    if parm='Prm7' then parm='Prm07';
    if parm='Prm8' then parm='Prm08';
    if parm='Prm9' then parm='Prm09';
    if parm='Prm10' then parm='Prm10';
    if parm='Prm11' then parm='Prm11';
    if parm='Prm12' then parm='Prm12';
    if parm='Prm13' then parm='Prm13';
    if parm='Prm14' then parm='Prm14';
    if parm='Prm15' then parm='Prm15';
    if parm='Prm16' then parm='Prm16';
    if parm='Prm17' then parm='Prm17';
    if parm='Prm18' then parm='Prm18';
    if parm='Prm19' then parm='Prm19';
    if parm='Prm20' then parm='Prm20';
run;

proc sort data=next_1a;
    by parm;
run;

data next_2(drop=effect);
    merge next_1a( in=in1a)
          next_1  (in=in1);
    by parm;
    if in1a;
    parm=effect;
    rename parm=_name_;
run;

data next_3;
    set next_2;
    if _name_='SCALE' then delete;
run;

data next_4;
   length _name_ $25;
    _name_= 'ESTIMATE';
    output;
run;
```

```
data next_5;
    set next_4
        next_3;
run;

proc print data=next_5;
    title Input dataset--GENMOD;
run;
%end;

%else %do;
data next_5;
    set &covdsn;
run;

proc print data=next_5;
    title Input dataset--LOGISTIC/PHREG;
run;
%end;

%if (next_5 ne ) %then %do;

%let __stop=0;

proc iml;
    use next_5;
    read all var {_name_} into _varname;

    _nrvname=nrow(_varname);

    if (_nrvname>1) then do;
        _varnam2=_varname(|2:_nrvname, |);
        nmissing=j(nrow(_varnam2),1,.);
        labels={"EIGENVAL","CONDINDX","        "};
        _varnam2=labels//_varnam2;
        free _varname labels;
        read all var _num_ into varcov(|colname=_nvname|);
        _nrcvc=ncol(varcov);
        lastvnam=_nvname(|1,_nrcvc|);
        if (lastvnam="_LNLIKE_") then
varcov2=varcov(|2:_nrvname,1:_nrcvc-1|);
        if (lastvnam^="_LNLIKE_") then varcov2=varcov(|2:_nrvname,|);

%* If the covariance matrix is from GENMOD using the repeated measured
design, ;
%* then the lower diagonal will have the correlations and the upper
diagonal will have;
%* the covariances. The next section of code replaces the lower
diagonal with the upper;
%* diagonal to make a symmetric matrix.  If the matrix is symmetrical
already, then the;
%* next section of code will not affect anything.;

        vc2_c=ncol(varcov2);
        vc2_r=nrow(varcov2);
        do cl=1 to vc2_c;
```

```
            do rw=1 to vc2_r;
              varcov2(|rw,cl|) = varcov2(|cl,rw|);
            end;
        end;

        print varcov2;

        free varcov _nrcvc lastvnam vc2_c vc2_r cl;
        covbinv=inv(varcov2);
        scale=inv(sqrt(diag(covbinv)));
        r=scale*covbinv*scale;
        free covbinv scale;
        call eigen(musqr,v,r);
        free r;
        srootmus=sqrt(musqr);
        ci=1/(srootmus/max(srootmus));
        phi=(v##2)*diag(musqr##(-1));
        sumphi=phi(|,+|);
        pi=phi#(sumphi##(-1));
        free phi sumphi srootmus v;
        final=(musqr||ci||nmissing||pi`)`;
        free pi musqr ci nmissing;
        _ncfinal=ncol(final);
        _nrfinal=nrow(final);
        final2=j(_nrfinal,_ncfinal,0);
        _ncfp1=_ncfinal+1;
        __vdp="VDP";
        do i=1 to _ncfinal;
            final2(|,_ncfp1-i|)=final(|,i|);
            x=char(i,3);
            y=compress(concat(__vdp,x));
            if i=1 then _vdpname=y;
                else _vdpname=_vdpname||y;
        end;
        free final _nrfinal _ncfinal i x y;
        create final2 from final2(|rowname=_varnam2 colname=_vdpname|);
        append from final2(|rowname=_varnam2|);
        free _varnam2 _vdpname final2;
    end;
    if (_nrvname=1) then do;
        x="1";
        call symput("__stop",left(x));
        print " ";
        print
"************************************************************";
        print "You need to specify the covout option";
        print "in either proc logistic or proc phreg.";
        print "This program will not calculate collinearity
diagnostics.";
        print
"************************************************************";
        print " ";
    end;
    quit;
run;

%if (&__stop eq 0) %then %do;
```

```
proc print data=final2 label noobs;
    id _varnam2;
    title8 "Collinearity diagnostics for nonlinear models using";
    title9 "the information matrix:  Eigenvalues, Condition Indexes,";
    title10 "and Variance Decomposition Proportions (VDPs)";
    label _varnam2="VARIABLE";
run;
%end;

%end;
%else %do;
   %put;
   %put "******************************************************";
   %put "When you invoke this macro, you have to specify the name";
   %put "of a SAS data set that contains the variance-covariance";
   %put "matrix from LOGISTIC, PHREG, or GENMOD.";
   %put;
   %put "For more information, see the macro code (comments";
   %put "are included with instructions.";
   %put "******************************************************";
   %put;
%end;

proc datasets;
    delete next_1 next_1a next_2 next_3 next_4 next_5;
run;
quit;

%mend collin;
```

References

1. Hotez P, Bottazzi M, Franco-Paredes C, et al. The neglected tropical diseases of Latin America and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. *PLoS Neglected Tropical Diseases* 2008;2(9):e300.
2. Sabesan S, Raju H, Srividya A, et al. Delimination of lymphatic filariasis transmission risk areas: a geo-enviromnental approach. *Filaria Journal* 2006;5(1):12.
3. Miller M, Barrett S, Henderson D. Infectious diseases. *Disease Control Priorities Project*. Washington: The World Bank, 2006:322.
4. Michael E, Bundy D, Grenfell B. Re-assessing the global prevalence and distribution of lymphatic filariasis. *Parasitology* 1996;112:20.
5. Weil G, Ramzy R. Diagnostic tools for filariasis elimination programs. *TRENDS in Parasitology* 2007;23(2):5.
6. Boyd A, Won K, McClintock S, et al. A community-based study of factors associated with continuing transmission of lymphatic filariasis in Leogane, Haiti. *PLoS Neglected Tropical Diseases* 2010;4(3):e640.
7. Progress Report 2000-2009 and Strategic Plan 2010-2020 of the global programme to eliminate lymphatic filariasis: halfway towards eliminating lymphatic filariasis. World Health Organization, 2010.
8. Research on Rapid Geographical Assessment of Bancroftian Filariasis. *TDR/TDF/COMDT/982*: World Health Organization, 1998.
9. Vanamail P, Subramanian S, Srividya A, et al. Operational feasibility of lot quality assurance sampling (LQAS) as a tool in routine process monitoring of filariasis control programmes. *Tropical medicine & international health : TM & IH* 2006;11(8):1256-63.
10. Ramzy R, El Setouchy M, Helmy H, et al. The impact of single-dose diethylcarbamazine treatment of Bancroftian filarisis in a low-endemicity setting in Egypt. *The American Society of Tropical Medicine and Hygiene* 2002;67(2):5.
11. Ramaiah K, Thiruvengadam B, Vanamail P, et al. Prolonged persistence of residual Wuchereria bancrofti infection after cessation of diethylcarbamazine-fortified salt programme. *Tropical Medicine & International Health* 2009;14(8):870-6.
12. Dreyer G, Addiss D, Noroes J. Does longevity of adult increase with decreasing intensity of parasite transmission? Insights from clinical observations. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2005;99(12):883-92.
13. Stolk W, de Vlas S, Habbema D. Advances and challenges in predicting the impact of lymphatic filariasis elimination programmes. Geneva: World Health Organization, 2005:13.
14. Gambhir M, Bockarie M, Tisch D, et al. Geographic and ecologic heterogeneity in elimination thresholds for the major vector-borne helminthic disease, lymphatic filariasis. *BMC Biology* 2010;8(1):22.

15. Swaminathan S, Subash P, Rengachari R, et al. Mathematical models for lymphatic filariasis transmission and control: Challenges and prospects. *Parasites & Vectors* 2008;1(1):2.
16. Grady C, Beau de Rochars M, Direny A, et al. Endopints for lymphatic filariasis programs. *Emerging Infectious Disease* 2007;13(4):3.
17. Epidemiological Profiles of Neglected Diseases and other Infections Related to Poverty in Latin America and the Caribbean. *Prevention and Control of Communicable Diseases*. Washington, DC: Pan American Health Organization, 2009:123.
18. Beau de Rochars M, Milford M, Jean Y, et al. Geographic distribution of lymphatic filariasis in Haiti. *American Journal of Tropical Medicine and Hygeine* 2004;71(5):4.
19. Leite A, de Lima A, Leite R, et al. Assessment of family and neighbors of an individual infected with *Wuchereria bancrofti* from a non-endemic are in the city of Maceió, Brazil. *Brazilian Journal of Infectious Disease* 2010;14(2):4.
20. Washington C, Radday J, Streit T, et al. Spatial clustering of filarial transmission before and after a mass drug administration in a setting of low infection prevalence. *Filaria Journal* 2004;3(3):14.
21. Davis C, Hyde J, Bangdiwala S, et al. An example of dependencies among variables in a conditional logistic regression. In: Moolgavkar S, Prentice R, eds. *Modern Statistical Methods in Chronic Disease Epidemiology*. New York: John Wiley & Sons Inc., 1986:7.
22. Life Cycle of *Wuchereria bancrofti*. Atlanta: Centers for Disease Control and Prevention, 2009.
23. Haiti: population density by commune. *Map Action*. Little Missenden: Relief Web, 2008.
24. Haiti Vegetation and Land Use Map 1970. Central Intelligence agency, 1970.