INVESTIGATING FACTORS IN THE SPREAD OF LEPROSY THROUGH

HOUSEHOLD CONTACTS

by

Mounika Abbareddy

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GRADUATE SCHOOL OF PUBLIC HEALTH

This essay is submitted

by

Mounika Abbareddy

on

April 26, 2019

and approved by

Essay Advisor

Jeremy J. Martinson, DPhil Assistant Professor Infectious Diseases and Microbiology Graduate School of Public Health University of Pittsburgh

Essay Reader

Joanne Russell, MPPM Director Center for Global Health Graduated School of Public Health University of Pittsburgh Copyright © by Mounika Abbareddy

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Mounika Abbareddy, MPH

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ABSTRACT

Leprosy is a disease that has been recorded throughout history and is caused by the bacterium Mycobacterium leprae. Leprosy is still very prevalent in India, where more than half of new cases can be found. The bacterium can be transmitted through droplets or close contact. The purpose of this essay is to examine the transmission of leprosy to household contacts by examining previous research through a literature review and analyzing data that has been collected previously. The public health importance of this essay is that by analyzing the transmission, interventions can be designed to stop this from occurring. Well planned and successful interventions can help to reduce the burden of the disease and will help in the path to its eradication. This research consisted of a literature review and analysis of previously collected data. The literature review showed that males were more susceptible to leprosy and that a closer genetic relation increases the risk of leprosy transmission. More research is needed to discover why males are more susceptible to leprosy than females. Data analysis also showed that most cases occurred among contacts that that had closer genetic relationships with the index cases. The data also showed that the duration between diagnoses of the index and contact cases ranged from 1 year to 16 years. This shows that for successful contact tracing interventions, monitoring

should be done for at least 5 years to detect undiagnosed cases. That way, many of the cases that go unnoticed will be diagnosed early on and can be treated early. This will reduce the risk that this new case will transmit it to other contacts.

PREF	ACE	Х	
1.0	INTR	ODUCTION1	
	1.1	HISTORY OF LEPROSY1	
	1.2	PREVALENCE	
	1.3	TRANSMISSION	
	1.4	SIGNS AND SYMPTOMS	
	1.5	DIAGNOSIS AND TREATMENT4	
	1.6	PREVENTION5	
	1.7	WHO RESPONSE: GLOBAL LEPROSY STRATEGY 2016-2020 6	
	1.8	OBJECTIVES AND PUBLIC HEALTH IMPORTANCE7	
2.0	METHODS		
	2.1	LITERATURE REVIEW	
	2.2	STUDY DATA9	
3.0	RESULTS11		
	3.1	LITERATURE REVIEW 11	
	3.2	STUDY DATA13	
4.0	DISCUSSION18		
	4.1	LITERATURE REVIEW 18	
	4.2	STUDY DATA19	
5.0	CON	CLUSION	
BIBIC	OLOGE	RAPHY	

TABLE OF CONTENTS

LIST OF TABLES

Table 1. Leprosy Incidence in Some Countries. 2

LIST OF FIGURES

Figure 1. Literature Review Flowchart	8
Figure 2. Map of Indian States	9
Figure 3. Demographic Charts (A, B, C, D, E)	.14
Figure 4. Relation and Duration (A, B)	. 16

LIST OF ACRONYMS

- WHO World Health Organization
- PB paucibacillary
- MB multibacillary
- GIS geographic information system

PREFACE

ACKNOWLEDGMENTS

I would first like to thank my thesis advisor Jeremy Martinson, DPhil of the IDM department in the Graduate School of Public Health at the University of Pittsburgh. I would also like to acknowledge Joanne Russell, MPPM of the Center for Global Health at the Graduate School of Public Health at the University of Pittsburgh as the second reader of this thesis, and I am gratefully indebted to her for her very valuable comments on this thesis.

I would also like to thank the research team at the LEPRA Society in Hyderabad, India for teaching me about leprosy and the current extent of this problem in India.

1.0 INTRODUCTION

Leprosy, also called Hansen's disease, is a chronic infectious disease. It is caused by an acid-fast, rod-shaped bacteria known as *Mycobacterium leprae*.¹ Leprosy has a long history, but much about it is still unknown. It is still endemic in many areas of the world. Untreated leprosy can cause many complications and disability. In 2015, the World Health Organization has created a plan to help bring the world closer to being leprosy-free, but there is still a lot of research to be done if we want to accomplish this. The LEPRA Society does research in all areas of leprosy transmission, infection, and prevention. Research being done there inspired the topic of this essay. The aim of this paper is to see if there are any trends in leprosy transmission to household contacts and if any one population is more at risk than the other.

1.1 HISTORY OF LEPROSY

Leprosy has been described in many ways throughout history. Ancient civilizations, including those of China, Egypt, and India, has descriptions of a disease that seems to cause the same symptoms as leprosy.² The symptoms of the disease are visible as they mostly affect the skin. For this reason, people affected with leprosy have been discriminated against throughout history. In medieval times, those with leprosy would often be shunned from society and would even be buried in separate areas, away from the normal cemetary.³

The leprosy bacterium was discovered in 1873 by Gerhard Armauer Hansen, a Norwegian physician.⁴ He discovered the bacteria when he was examining skin nodules from patient biopsies.⁴ Hansen studied this bacterium and believed contact with impoverished people was the reason that it spread.⁴ He helped to enact laws that required poor people to live in separate homes in communities separate from the rest of society.⁴ Another law in Norway

required those affected with leprosy (referred to as lepers at the time) to live separately from their community and families.⁴ Leprosy has been studied and understood better since then, but there is still much we do not know about this debilitating disease.

1.2 PREVALENCE

The World Health Organization has been working for many years to reduce the incidence of leprosy. In 2000, it was declared that leprosy was no longer a global public health problem, as the prevalence has dropped to below 1 per 10,000 population.⁵ In 1983, the prevalence rate of leprosy was 21.1 per 10,000 population.⁵ By the end of 2015, this number has dropped down to 0.29 per 10,000 population.⁶ Although leprosy has decreased drastically worldwide, there are still quite a few countries where it is still endemic, such as Ethiopia, Nigeria, India, Nepal, and Brazil.⁵

Tuble II Deprosy meddenee in Some Countries.			
Country	Number of new cases reported in 2012 ⁶		
Nepal	3,492		
Ethiopia	3,776		
Nigeria	3,805		
Brazil	33,303		
India	134,752		

Table 1. Leprosy Incidence in Some Countries.

Leprosy is still a major problem in India. The prevalence of leprosy in India is 0.81 per 10,000.⁶ Although this is still less than the 1 per 10,000 threshold, it is still significantly higher than the global prevalence.⁶ The number of new cases in the world in 2015 was 210,758.⁶ India reported a total number of 86,028 new cases that year, approximately 60% of the total number of new leprosy cases.⁶

1.3 TRANSMISSION

Leprosy is not as easily transmitted as previously believed, and as previously stated by Dr. Hansen. It has been suggested that many people are immune to it and that only about five percent of the total population is actually susceptible to leprosy.⁴ Whether this is because of a genetic reason, environmental factors, or is just based on looking at the percent of the population that is affected is not known and needs to be researched. Leprosy can either be transmitted through droplets or through prolonged contact.⁷

Transmission of this disease is not wholly known. Droplets from infected people's coughs or sneezes can infect a healthy person, just as in tuberculosis.⁷ However, it has been hypothesized that close, prolonged contact with a person affected with leprosy can spread the disease.⁷ Research has shown that shaking hands or just sitting next to each other for short amounts of time will not transmit the disease.⁷ Prolonged contact over a few months it most likely needed for transmission to occur.⁷ More research is needed to see how important contact transmission is to the spread of the disease.

Animals, like monkeys, can sometimes be a reservoir for the disease. In the United States, armadillos are naturally infected with the leprosy bacterium. There is only about a 10% risk for transmission to humans.⁷

1.4 SIGNS AND SYMPTOMS

There are several of leprosy, each defined by the type and number of skin sores. Each form can have different symptoms. Tuberculoid leprosy is a milder form of the disease. One or a few patches of skin sores are found in this type and a little nerve damage may occur.² This type is less contagious than lepromatous leprosy. In lepromatous type, skin sores are prevalent, and

many other symptoms are also present. Nerve damage is more widespread.² In borderline leprosy, a person may have symptoms of both tuberculoid and lepromatous leprosy.² While the exact prevalence of each type is not known, lepromatous is more common because it is more contagious.

Symptoms in leprosy can take a while to appear. Someone can be infected with leprosy for years before symptoms even start to develop. Leprosy mainly affect the skin, nerves, and mucous membranes.⁸ These symptoms can be seen in all types, but to a varying degree. The most common skin symptom is discolored or lighter patches of skin.⁸ They can grow to be thick and dry patches of skin.⁸ On the feet, ulcers can usually develop, especially if not taken care of properly.⁸

A symptom in the nerves that is seen most often is the presence of enlarged nerves.⁸ This can be felt for by a doctor, especially around the elbow and knee area.⁸ Nerves can also be affected by being numb, weak, or stiff.⁸ Nerves around the eyes can be affected and lead to blindness. Symptoms of the mucous membrane include nosebleeds.⁸

If leprosy goes untreated, complications can occur including paralysis, blindness, ulcers that can't be healed, chronic pain in nerves, and burning feeling of the skin. Hands can become paralyzed in a folded, grasping position.⁸

1.5 DIAGNOSIS AND TREATMENT

For treatment to be done, leprosy needs to first be classified. Clinically, the number of skin lesions and number of enlarged nerves are used to classify leprosy.⁹ In laboratory testing, skin smear results are used. If a discolored patch of skin is observed, the doctor will take a sample of it, which will then be tested in a laboratory.⁹ If no bacteria is detected in this skin smear test, it is

paucibacillary leprosy (PB).² A positive skin smear test indicates that it is multibacillary leprosy (MB).²

Treatment for leprosy consists of multidrug therapy. The length and number of antibiotics will vary depending on the classification and progression of the disease. The antibiotics used are dapsone with rifampicin.⁹ Clofazimine can sometimes be added for MB leprosy. The treatment can usually last between six months to one year, depending on the type and severity.⁹

Other drugs, such as prednisone, can be supplemented to help with nerve pain.² Thalidomide can sometimes be used to treat the skin lesions, but it is not highly recommended since it suppresses the immune system and can cause birth-defects.² The purpose of these antibiotics is to kill the bacteria that causes the disease. If treatment is started late, the complications mentioned in section 1.4 can occur. Once complications occur, multidrug therapy cannot undo the damage that has been done. This is a reason why leprosy can be so serious. It has the ability to cause lifelong disability if not treated on time.

1.6 PREVENTION

There is no vaccine or pre-exposure therapy available for the prevention of leprosy. The best way to prevent from getting leprosy is by controlling contact with those who have been diagnosed.¹⁰ Since leprosy can be spread by droplets or close prolonged contact, maintaining a slight distance from someone diagnosed with leprosy can reduce risk of developing leprosy from them. Keeping distance does not need to be interminable, just as long as they are contagious and on the therapy. Those who travel to places where leprosy is endemic need to be aware of it and need to make sure that they are not exposed to the disease.¹⁰ Bringing it back with them to their home country can increase its spread in that country.

As the transmission and infectivity are not well known, it has been difficult to create a vaccine for the disease. Also, since the disease itself is not highly contagious, creating a vaccine isn't the most feasible option to controlling its spread.¹⁰

1.7 WHO RESPONSE: GLOBAL LEPROSY STRATEGY 2016-2020

In 2016, the World Health Organization launched a response to eliminating leprosy from the world. It is called the "*Global Leprosy Strategy 2016-2020: Accelerating towards a leprosy-free world*." ¹ The main goals of this are to reduce incidence of leprosy worldwide, especially in children, and to reduce the amount of disability caused by leprosy infection. There are 3 pillars and 3 main targets to this strategy.

The first pillar is to "strengthen government ownership, coordination, and partnership." ¹ This pillar includes things like improving surveillance, health coverage and availability, and having enough resources for leprosy programs. The second pillar is to "stop leprosy and its complications" ¹ and involves increasing awareness, improving treatment adherence, and promoting early case detection. The third pillar is to "stop discrimination and promote inclusion." ¹ One of the biggest problems with leprosy, as discussed previously, is that it has always been a disease that has shunned people from regular society. Increasing education and awareness in communities and working to help change laws discriminating against people affected by leprosy can help work towards this pillar of the strategy.

The three targets to the WHO leprosy strategy are to (1) have zero disabilities among new pediatric patients, (2) have an incidence rate for grade-2 disability cases less than 1 per 1 million people, and (3) have no countries with legislation that discriminate against people affect by leprosy.¹ There are still approximately 20 countries with laws against leprosy patients. India

itself has many different regional laws that discriminate against people affected by leprosy. These targets go along with the pillars and are reasonable goals if we are to get closer to eradicating leprosy and its burden on people's health.

1.8 OBJECTIVES AND PUBLIC HEALTH IMPORTANCE

The objective of this essay is to determine if household contacts have a greater risk of being infected with leprosy. The first part of this essay will be to examine previous literature and research that has been done on this subject. The second part of the essay is to analyze data that was collected for a previous study to see if it supports the research or if there is something else that needs to be investigated for its effect on the spread of leprosy through contacts.

This is of great public health importance because, by assessing the impact of contact transmission in the spread of leprosy and the risks associated with it, recommendations for programs can be made. If it is found that contacts are a major group that get infected with leprosy, public health programs that aim to eradicate leprosy would need to include ways that trace contacts and prevent further transmission. Eradication of this disease can be sped up through this research.

2.0 METHODS

2.1 LITERATURE REVIEW

A Google Scholar search was performed using the following search: "leprosy AND contacts OR household." Only peer-reviewed articles were included in the search. There was no restriction as to the publication date. The articles found through this search were then searched for through the University of Pittsburgh library website. The articles were downloaded and examined for their relevance to this study. Those that were more immunological, or treatment-based were excluded.

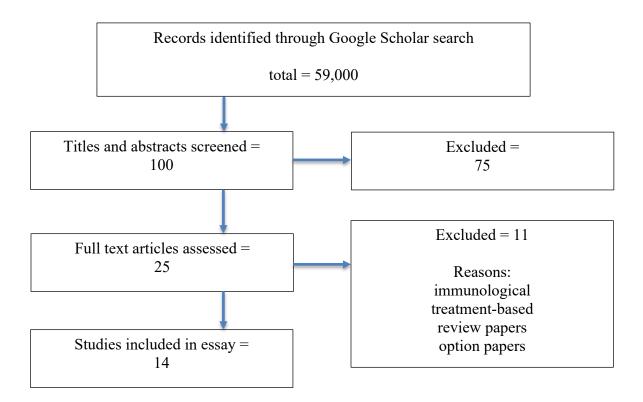


Figure 1. Literature Review Flowchart.

2.2 STUDY DATA

The data used had been collected for a previous study done by LEPRA in India, in which patients who were removed from treatment were revisited and interviewed about their current condition. Patients who were removed from treatment between 2005 and 2012 were included in the survey (identified as the index cases). These patients had records in clinics in 4 districts, 2 in Telangana and 2 in Odisha. These states are shown in the map below, in Figure 2. Retrospective data, demographic data, current problems, and information on contacts were collected. The patients were interviewed about their previous and current condition, and about the people with whom they come into contact. The contacts of the index case that has also been diagnosed with leprosy are identified as contact cases. Information on the relationship between the index case and contact cases was also collected, as well as the approximate data of diagnosis for the contact case.



Figure 2. Map of Indian States.²⁵ Data was collected from the states of Telangana and Odisha.

This data was reviewed and analyzed specifically for the index cases with contacts diagnosed with leprosy as compared to the contact cases. The data was cleaned and analyzed using Microsoft Excel, STATA, and R studio. The secondary attack rate was calculated. Demographic data and clinical features of the index cases were examined for possible patterns and correlations. The familial relationship between the cases was also examined, as was the time between diagnoses.

3.0 **RESULTS**

3.1 LITERATURE REVIEW

Fourteen articles were found to have pertinent information to this study. All of the articles relate to leprosy and contacts in the household. The publication dates range from 1987 all the way to 2019. Most studies took place in India, while some were in neighboring or nearby countries like Bangladesh and China. The articles are summarized below and discussed in detail in the Discussion section.

In 1987, Ashamalla¹¹ published a study in the International Journal of Dermatology, where 89 families, consisting of at least one person affected by leprosy, were examined. Out of these, 2 families were found where both members of a couple had leprosy, 7 cases were found where the father and son had leprosy, and 1 case was found where the mother and son had leprosy. A study by Fine et al.¹² in 1997 did a detailed analysis of household contacts. It was a longitudinal study done in Malawi and it was found that the risk of getting leprosy is higher in younger contacts than older contacts and in males more than females. However, a study by Moet et al. in 2006¹³ found that older contacts have a higher risk of becoming infected with leprosy. This study also found that a close household and genetic relationship means an increased risk of getting leprosy. In 2004, Douglas et al.¹⁵ examined the serology of patients to determine if it can be used as a method to identify if people in the household have a risk of getting leprosy. They found that the seropositivity rate was higher in contacts that lived where new cases were detected than for contacts in household where there were no new cases.

An observational study in 2008 by Fischer et al.¹⁶ used GIS to map 4 villages in Bangladesh. They were looking for spatial patterns and clustering of leprosy cases. They did not find a significant evidence of clustering. From their study, they found that spatial analysis may be more useful at a regional level rather than at a village level. Fischer et al.¹⁷ also conducted a study in 2010 where they tested 18 different scenarios of households with different susceptibilities to the disease. They found that clustering is seen more in households due to increased transmission but is not affected by susceptibility to leprosy.

In 2014, Smith and Aerts¹⁸ published a study in *Leprosy Review* where they examined contact tracing and other prevention strategies. They observed the advantages and disadvantages of contact tracing and chemoprophylaxis, separately and when combined. It was found that combining the two can have a good affect in discovering new infections and then limiting their spread.

Shumin et al.¹⁹ also examined contacts in their study in China. This was a retrospective study looking at cases over an 11-year period. They found that contact tracing, if it had been done at the time, could have identified cases of leprosy that had not been diagnosed on time. Richardus et al.²⁰ conducted a similar retrospective contact study in Bangladesh and Thailand. They looked at data over a 10-year period. They found that low endemic areas have a higher number of new cases have household contacts with leprosy than in high endemic areas. A retrospective study done in China by Shen et al.²¹ also shows that contact tracing is a good method for case detection in low endemic areas. In 2017, Nair²² did a similar retrospective study in India, where the prevalence of leprosy in families was examined, along with clinical features of leprosy. This was an 18-year retrospective study. The prevalence was found to be 5.44% and

most people (71%) belonged to the lower socioeconomic class. Most of the cases were found in males (about 62%) and in only 2% of cases were both members of a couple affected by leprosy.

Two literature reviews of leprosy transmission risks have been done. In 2004, Moet et al.²³ found that the closer a person is to someone affected by leprosy, the greater risk they have of becoming infected themselves. Similarly, a review done by Joyce²⁴ in 2012 found that a closer genetic relationship combined with more close contact time will increase risk of leprosy transmission. It was found that the risk of transmission is lower for spouses than for blood relatives.

3.2 STUDY DATA

There were 913 index cases in this data set. An index case, as stated previously, is an individual diagnosed with leprosy who was removed from treatment and was interviewed for the study. These patients had a total of 3540 contacts. One hundred and twenty-two of the index cases had contacts that were also diagnosed with leprosy (referred to as a contact case). Of these, 86 had one contact diagnosed with leprosy, 31 had two contacts diagnosed, and five had three contacts diagnosed. This amounted to a total of 163 contact cases. The secondary attack rate was calculated from the number of contact cases and total number of contacts and was found to be 4.576%.

The data were collected from four different districts, two from each state (Telangana and Odisha). There was a total of 340 index cases in Telangana, with 1008 total contacts. Of these, 72 had been diagnosed with leprosy, resulting in a secondary attack rate of 7.14%. Odisha had a total of 573 index cases and 2532 total contacts. Of these, 91 had been diagnosed with leprosy, resulting in a secondary attack rate of 3.59%.

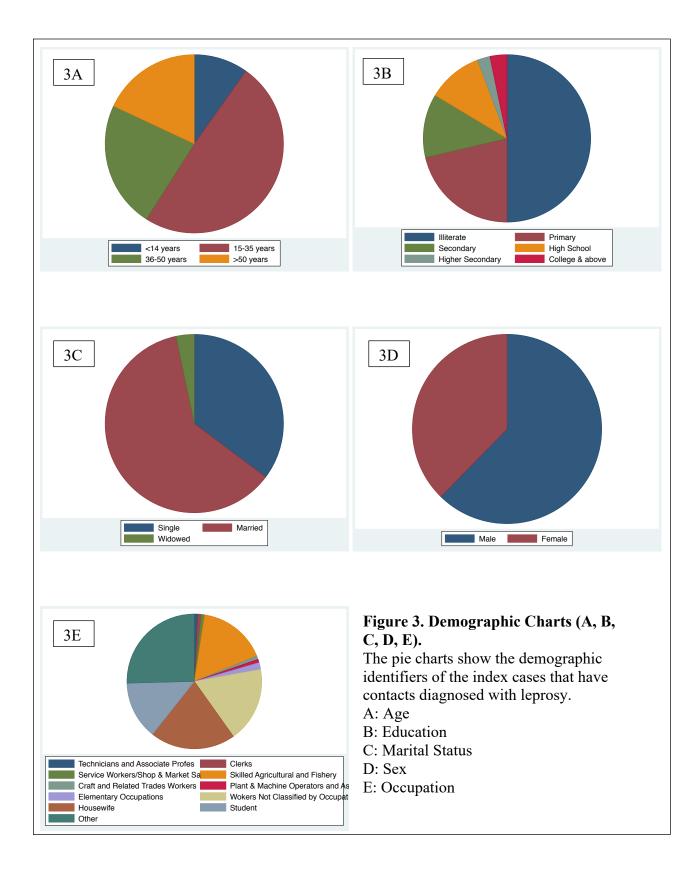


Figure 3 shows the demographic data for those index cases that have a contact that has been diagnosed with leprosy, a total of 122 cases. Figure 3A shows the age of the index cases. Ten percent are less than 14 years of age; 50% are between the ages of 15 and 35; 23% are between the ages of 36 and 50; and 18% are older than 50 years. Education is shown in Figure 3B. Fifty percent of the index cases are illiterate; 21% have completed primary school; 12% have completed secondary school; 10% have completed high school; 3% have completed higher secondary school; and 3% have completed college or beyond. Figure 3C shows marital status of the index cases. Sixty-one percent are married, 35% are single, and 3% are widowed. Sex is shown in Figure 3D. Of these index cases, 77 (63% are male) and 45 (37%) are female. Finally, 3E shows occupation of the index cases. Twenty percent are housewives, 18% are workers not classified by occupation, 16% are skilled agricultural and fishery workers, 13% are students, and 25% fall into the other category.

Sex ratio was also calculated in other scenarios and comparisons. The total number of index cases was 913, 569 (62%) of whom were male and 344 (38%) were female. Among the 77 male index cases that also had contacts with leprosy, 63 of their 103 contact cases (61%) were male and 39 (38%) were female. Among the 45 female index cases that also had contacts with leprosy, 41 of their 60 contact cases (68%) were male and 18 (30%) were female.

Clinical features of the cases were examined. Although a few features are more common than others, there is no significant correlation between the features and if transmission occurred to the contacts.

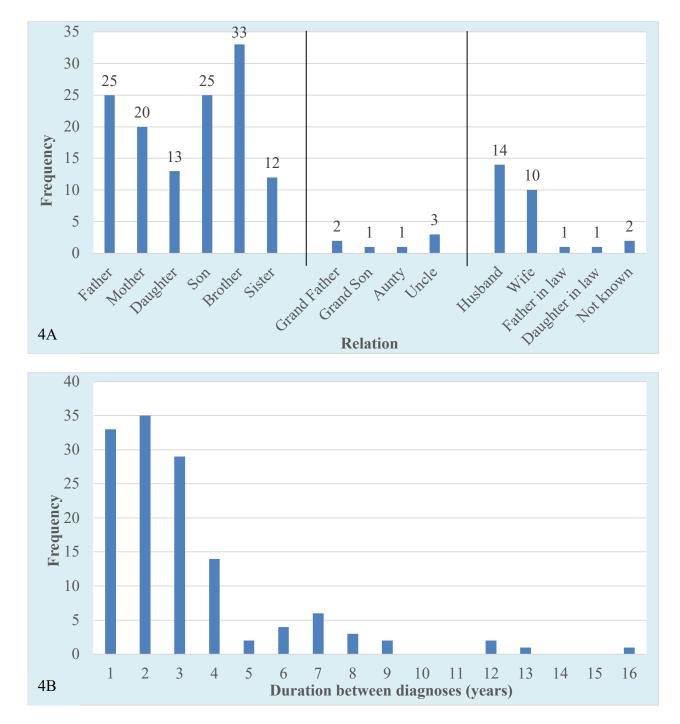


Figure 4. Relation and Duration (A, B).

4A: shows the relationships between the contact and index cases4B: shows the duration (in years) between the diagnoses of the contact and index cases.

The relationship between the index and contact cases was identified. These relationships and their frequencies can be seen in Figure 4A above. The coefficients of relationship were also identified. Parent-offspring pairs have a coefficient of relationship of 50%. This relationship was identified in 83 of the 163 contact cases. Siblings also have a coefficient of relationship of 50%, a relationship which was identified in 45 cases. Basically, a coefficient of relationship of 50% was identified in a total of 128, or about 78.5%, of cases. These cases can be seen in the first section of the figure. The first six bars in the figure are part of this section. The frequency of these bars are a lot higher than those in the other sections.

The duration between the diagnoses of the index and contact cases was also measured. The frequencies of the number of years between diagnoses can be seen in Figure 4B above. For reference, 1 means between 0 and 1 year, 2 means between 1 and 2 years, and so on. Thirty of the contact cases had data missing as to the diagnosis date, so are not included in the figure above. As shown in the figure, a majority of the cases had between 0 and 3 years between diagnoses, but there are still a few that had about a 6, 7 or even 16-year gap.

4.0 **DISCUSSION**

4.1 LITERATURE REVIEW

From the studies done by Ashamalla¹¹, Fine et al.¹², Moet et al.¹³, Sales et al.¹⁴, and Douglas et al.¹⁵, we can see initial evidence of leprosy transmission between household contacts. We can also see a trend of more cases in males than in females. The contradicting results for age as a risk factor show that more research is needed in that area. Both the studies done by Fischer et al.^{16,17} show that mapping and tracing can be good ways to find leprosy cases.

Smith and Aerts¹⁸ found that chemoprophylaxis can reduce risk of leprosy transmission and that contact tracing can be useful in many scenarios. Combining these two strategies can be a possible future intervention. Using chemoprophylaxis to treat contacts of a diagnosed leprosy case can be useful to reduce the risk for those contacts in being infected with leprosy themselves.

Retrospective studies have been a popular method in the study of leprosy and its transmission. This is because leprosy can have a long incubation period and so its transmission can be hard to study. The studies described above show the value of contact tracing. The study by Nair shows several possible risk factors associated with increased risk of transmission. These risk factors can be good variables to study in the future.

The literature reviews that have been done aren't comprehensive, but they do reemphasize the fact that there is an increased risk of getting leprosy with increased contact. They also show that there seem to be some sort of genetic connection to transmission, as blood relatives have a higher risk than spouses. This is also another point that should be further researched.

4.2 STUDY DATA

The secondary attack rate that was calculated came out to be 4.576%, which is close to the prevalence rate of 5.44% found by Nair²². The secondary attack rate shows the spread of an infection in contacts of the main index case. It can be interpreted as the probability that the infection will occur in the contacts. Basically, the number calculated indicates that approximately 4 of every 100 contacts will become infected with leprosy. This number is higher than the prevalence of leprosy in India. The secondary attack rates of each district were also calculated. The district of Telangana has a secondary attack rate that is much higher than that of Odisha. This indicates that there is some factor in the population of Telangana that make the people there more at risk for leprosy.

Figure 3 shows the demographic information for the index cases with contacts that have been diagnosed with leprosy. Most of the index cases, approximately 83%, are below 50 years of age. It was also found that half are illiterate, and more than half are married. The occupations that showed up the most were housewife, farmer, fishery worker, and student. This information shows that those of lower socioeconomic class are more at risk. This is as was expected. Those who are in a lower socioeconomic class usually live in small houses. Many people will live and sleep in the same room. This means that they would have more prolonged contact with each other. If one is infected with leprosy, then everyone else in the household has a higher risk of getting leprosy.

The sex ratios of the index cases and the contact cases were found. Among the index cases 62% were male. The percentage of total male contacts, male contacts connected with the male index cases, and male contacts connected with the female index cases were all also around 60%. This shows that males seem to be more at risk of getting leprosy, supporting the literature

that was discussed previously. There is something that makes males more susceptible to leprosy. There is no evidence as to what might make them more susceptible. More research would be needed in this area in order to know if it is due to an environmental factor or a genetic factor.

The clinical features of index cases were examined. No significant correlation was found. The data from this study does not show any particular feature that makes people more susceptible to leprosy. More research is needed in this area.

Figure 4A shows the relationship between the index and contact cases. In 78% of the cases, they have a correlation of relationship of 50%. This means that in most of the cases, the index and contact cases are closely related genetically. This is in line with the literature and research done previously. Genetically related individuals seem to have a higher chance of becoming infected with leprosy. This may be because of increased contact between genetically related individuals.

Figure 4B shows the duration between diagnoses of the index and contact cases. The duration between diagnoses is consistent with the incubation period for leprosy. Although one and two years is a common duration, many contacts also go anywhere between 3 to 16 years before being diagnosed with leprosy. This indicates that follow-up visits with those who were diagnosed with leprosy and their contacts should occur every year for at least 5-6 years. Doing this will help get closer to goal of eradicating leprosy once and for all.

5.0 CONCLUSION

Leprosy is a disease that is still prevalent in the many countries of the world today. The literature shows that research has been done on different variables that may increase the risk of transmission of leprosy. There is a lot of research that has been done, but none of it shows a conclusive reason or method for the transmission of leprosy through contacts. There are still many questions that are raised through the data from the studies described in the literature review.

Future research needs to be done in all of areas analyzed from the data. Research on what increases the transmission of leprosy can be very helpful in stopping its spread. The data shows that the duration between diagnoses can be long. Therefore, interventions should include monitoring for at least 5-6 years after initial diagnosis. This can help to increase early detection of leprosy and reduce the burden and disability that may be caused from this disease.

By conducting more research into contact transmission and what makes increases its risk, interventions can be created that will be more successful at stopping the transmission of the disease. The goal for the WHO Global Leprosy Strategy is to, in the end, eradicate the disease and the burden cause from it. Doing this is of great public health importance. The literature review and data show that research on males and on the duration between transmission can be good places to start. By knowing exactly what increases the risk of transmission, those factors can be targeted, and the incidence of the disease can be reduced.

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