CHAPTER 2

REVIEW OF LITERATURE
This Chapter reviews the literatures based on applications of statistical methods in the epidemiological studies, the vaccination trial and the field of Leprosy.

2.1 VACCINATION

Vaccination is found out to be the best cost-effective method in public health services and saves millions of lives, mainly children. There is some belief through an earlier manuscript that the practice of inoculation may have originated in India and China before the 17th century. Smallpox is considered to be the first disease, people took effort to inoculate themselves from and for which a vaccine was discovered. Smallpox was a contagious and fatal disease which killed 300–400 million people during the 20th century alone [Lombard M. et al (2007)].

The British physician Edward Jenner invented a vaccine against cowpox and designed vaccine to inoculate humans from pathogen smallpox in 1796. Edward Jenner was extensively criticized, because it was considered unreligious to immunize a human with some substance from an infected animal. Since he had proved that cowpox eruption (postule) can be used for immunizing smallpox. However, the process of vaccination began during the 18th century [BBC 2014].

After several years, following his pioneering, Louis Pasteur invented a vaccine for protecting against Anthrax and Rabies. Consequently, immunizations were administered for not only preventing from infection, but also to elicit an immune response more rigorously with fewer hazards than further infection. By the end of the 19th century, immunization against rabies, cholera, plague and typhoid was developed and were commonly used in practice. With the development of technology, new vaccines were introduced better than the previous for the same
diseases such as malaria, HIV, etc., when more than one vaccine are available for a disease, the problem arises to evaluate and compare the their efficiencies. Several study designs, epidemiological and statistical methods were widely used in vaccine studies in this period.

2.1.1 Estimation of vaccine efficacy in Vaccination trials

In the early 20th century and during the end of the World War II, eminent statisticians and researchers were dynamically involved in developing a design and statistical method to evaluate the potency of these vaccines.

Generally, vaccine efficacy and vaccine effectiveness are estimated as

\[
VE = 1 - RR
\]

Where RR is the Relative Risk in the vaccinated group compared with unvaccinated group. Here a group can be represented as individuals or communities or population. In 1904, renowned statistician Karl Pearson had published a criticism in the issue of the *British Medical Journal*. It was about Anti-Typhoid Committee’s report on anti-typhoid vaccination information, in which they suggested usage of anti-typhoid inoculation. He re-analyzed the information and found that the correlation between disease and inoculation ranged from 0.021 to 0.445. The well-known statistician Major Green Wood and Udny Yule (1915) published this information in an article “The statistics of Anti-Typhoid and Anti-Cholera Inoculations and the interpretation of such statistics in general” in the “The Proceeding of the Royal Society of Medicine”. They analyzed the significance of inoculation’s effect against disease and mortality using Pearson’s chi-square and they
also suggested a general technique to analyze and interpret the data [Elizabeth Halloran Ira M. et al. (2009)].

Meanwhile, scientists (in 1920’s) began to develop advanced new vaccines against many infectious diseases, including smallpox, diphtheria, typhoid and tetanus. During that time, Pertussis (whooping cause) emerged as a chronic health problem for children and approximately 6,000 children died every year in the United States due to this disease. In 1930’s, Pearl Kendrick et al.began their research on Pertussis (whooping cough) vaccine at Michigan Department of Health laboratory in Michigan, USA and developed methods for growing the pertussis bacillus and invented a safe vaccine. Between 1934 and 1935 they had conducted the first large-scale, controlled clinical trial of pertussis vaccine and 1,592 participants (712 vaccinated and 880 unvaccinated) were involved in this trail. With the help of The Kent County Welfare, Relief Commission, they collected statistics on the prevalence of whooping cough and the number of children who had received ‘a treatment to prevent whooping cough’. According to that report, they found that only 4 individuals out of 712 had mild symptoms of whooping cough and 45 out of 880 unvaccinated suffered from that disease, which shows that the estimated vaccine efficacy rate is 89%[Carolyn G. Shapiro-Shapin (2010)].

In the early 1950’s, the advisory committee of the National Foundation for Infantile Paralysis (NFIP) decided to prove that killed virus Salk vaccine, developed by Jonas Salk at the University of Pittsburgh, United States had been both safe and capable of inducing high levels of the antibodies in the children. Paul Meier (1977) presented an article “The biggest public health experiment ever: The 1954 Field Trial of the Salk Poliomyelitis Vaccine”, based on the largest and expensive double
blinded randomized Poliomyelitis Vaccine trial in the USA. That experiment was conducted to assess the effectiveness of the Salk vaccine as a protection from paralysis or death from Poliomyelitis and around 5 million dollars was spent on that trial. Based on that trial, out of 1,829,916 participants, 7,49,236 received placebo, 428 were reported as cases. And among the vaccinated, 585 participants reported as cases. This trail confirmed that Salk vaccine provided sufficient effectiveness in preventing serious polio and is recommended to be introduced as a standard public health procedure. Numerous studies were developed based on this trail. Marcia Meldum (1998) published an article about this trial titled “A Calculated risk”: The Salk Polio vaccine field trials of 1954”, in which the author described the debate, problematic issue and how they successfully conducted this trial with public support. Harry Weaver, founder of NFIP spoke about this trial in his words “the practice of medicine is based on calculated risk….if we wait until more research is carried out, large numbers of human beings will develop poliomyelitis who might have been prevented from doing so”.

The Salk vaccine trial was conducted based on two statistical designs, the first one is *Observed control design* and the second one is *Randomized control design*. In the first one, participants were classified into vaccinated (called the treatment group) and not vaccinated (who received placebo called the control group) and in the second one the participants were randomly selected and were grouped as vaccinated and non vaccinated like Observed control design, but this experiment was double blinded that is neither the parents of a child in the study nor the doctors who treating the child knew which group the child belonged to. The results obtained from the trail were presented in Table-2.1 and was evaluated.
The effectiveness of the vaccine using conditional probability estimates is:

\[
\text{The effectiveness of vaccine} = \frac{\text{PUV}}{\text{PV}}
\]

Where PUV = paralyzed among unvaccinated (placebo)

PV = paralyzed among vaccinated.

**Table 2.1. The Salk Polio vaccine field trials of 1954, USA**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Study Group</th>
<th>Population</th>
<th>Polio Cases</th>
<th>False Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paralytic</td>
<td>Non Paralytic</td>
</tr>
<tr>
<td>Randomized Control</td>
<td>Vaccinated</td>
<td>200,745</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>201,229</td>
<td>115</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Not Inoculated</td>
<td>338,778</td>
<td>121</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Incomplete</td>
<td>8,484</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vaccinated</td>
<td>221,998</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td>Observed Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>controls</td>
<td>725,173</td>
<td>330</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Grade 2 Not</td>
<td>123,605</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Inoculated</td>
<td>9,904</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Source [1954 Polio Field Trial data]*
As a result of Salk vaccine trial, Jonas Salk’s vaccine was declared as effective in preventing paralytic poliomyelitis and the estimated effectiveness of the vaccine with statistical evidence is 71%.

In 1994, Polio was nearly eradicated from the United States, and on the other side, approximately 3,50,000 children were paralyzed with polio worldwide in 1988 and as a consequence of this “The Global Polio Eradication campaign” was initiated in the same year. After a lot of consistent prevention work against polio, cases had fallen to just over 1,200 globally in 2004.

D'arcy hart (1967) brought out a comparative study on six BCG vaccination trials held between 1936 and 1950 in the article named “Efficacy and Applicability of Mass B.C.G. Vaccination in Tuberculosis”. In this article, he gave the detail information of acceptance, mistrust and controversies on BCG vaccine worldwide; he listed out six different vaccination trial from 1936 to 1955 and statistical estimation of vaccine efficacies ranged from 14% to 80% from different parts of the world. He suggested that these variations of efficacies may occur due to certain factors like nutrition, the dose of tuberculin and natural immunity. Furthermore, he concluded that the full efficacy of vaccination will be experienced only by those free of all myco-bacterial infection and BCG will have an only moderate effect in developing countries.

In Netherland, a placebo controlled influenza vaccine trial was conducted on 374 children during the winter of 1967--68. A. Wesseltus-de casparis.A et al. (1972) carried out a study “Field trial with human and equine influenza vaccines in children: protection and antibody titers”. The children were randomly classified into
three groups according to their age and sex and were vaccinated with a vaccine containing 300 chicken cell agglutinating units (CCA) of A2/England/1/1966 or 300 CCA of A/equine 2/Miami/1963, or with a Placebo. They proposed this study to compare the antibody response and the protection rate of the vaccines, and to determine what level of circulating antibodies decreased the chance of acquiring an influenza A2 infection. The A2/1966 vaccine thus, gave a protection rate of 58% ($p = 0.02$) and the A/equine 2 vaccine reduced the attack rate by 19% ($p = 0.33$). They concluded that the influenza cases were equally distributed among the different age groups.

Initial studies were developed to estimate the effectiveness and potency of vaccine based on clinical trials. Later on, the methodologies of considering the factors such as age, sex, time since vaccination, region, etc., were considered while evaluating the vaccine effectiveness. In 1982, Marks J.S., et al. published a treatise on “Methodological issues in the evaluation of vaccine effectiveness”. They assessed the importance of methodological features in the design of field evaluation of vaccine efficacy and determined that several methodological approaches influence on the estimation of measles vaccine efficacy at the age of 12 vs. 15 months. They concluded that no single methodological feature clearly shows whether there is significantly improved vaccine efficacy with increasing in age at vaccination and they also suggested that there is a need for a detailed study on vaccine efficacy. In the same year, Campbell McIntyre et al (1982) published an article “Measles and Measles vaccine efficacy in a remote island population” based on a mass immunization campaign in measles, which was carried out between 24th February and 1st March 1969 in the Trust Territory of the Pacific Islands (TTPI). They
conducted a historical survey in 1976 on Ebeye, Marshall Islands and a review of the measles vaccine record of household contact cases of 258 children aged 1-9 years. They found that the overall vaccine efficacy rate is 83.5% and identified that the children who were immunized at the age of 12 or 13 months were 1.5 times more likely to get measles than those who were immunized at 14 months of age. In this study, they attempted to reveal that there was no evidence of any significant difference in immunity with the number of years since immunization.

Carol J. R. Hogue et al. (1983) suggested an odds ratio of cumulative – incidence case-control can be modified to obtain an accurate estimate of relative risk in any case of the incidence of the disease in the paper “Estimators of relative risk in case-control studies”. The authors suggested the modification of odds ratio were carried out based on four kinds of auxiliary information: overall probability of disease, the probability of disease in the unexposed population, the probability of disease in the exposed population, or overall probability of exposure. This paper persisted that the odds ratio approximation of relative risk in cumulative-incidence case-control studies are different from the direct estimate of relative risk of incidence-density. In 1983, another measles outbreak study was conducted in three Gambian villages in West Africa to estimate Measles mortality and vaccine efficacy in rural West Africa, Harry F Hull et al. (1983) worked on it. They identified that the attack rate in unvaccinated children aged 9--47 months was notably greater than vaccinated children of the same age group. They estimated that the vaccine efficacy was 37% and 89% for children of 6--8 months of age and 9 months or older, respectively. The study has also attempted to estimate vaccine efficacy using various regression models.
Walter A. Orenstein et al. (1985) suggested some epidemiology technique to estimate vaccine efficacy with a practical approach in their treatise “Field Evaluation of vaccine Efficacy”. They proposed that assessing the efficiency of vaccines is not only based on its potency, but also in the method of administering the vaccination, as well as the response of individual capability. Donna Brogan et al. (1987) have presented the methods for estimating vaccine efficacy for stratified designs. They suggested that various formulae to estimate attack rates, vaccine efficacy and the standard error of the estimated vaccine efficacy in an Expanded programme on Immunization surveys. This paper is also claimed as the extension of Orenstein (1985) paper “Field Evaluation of Vaccine Efficacy”.

Smith P.G. et al. (1984) published an article “Assessment of the protective efficacy of Vaccines against common diseases Case control and Cohort studies”. In this paper, they suggested the alternative approaches of randomized controlled trials as well as sociological surveys to evaluate vaccine efficacy. Also they proposed that these methods enable the comparison of the relative incidence rate of disease in vaccinated and unvaccinated population and facilitate to draw an inference about efficacy of vaccination programme. Kim-Farley R. J. et al. (1989) carried out the estimation of the efficacy of Oral Polio Vaccine (OPV) evaluated by the case exposure method using two different techniques and published the report “Poliomyelitis surveillance and vaccine efficacy in Bombay, 1982--87”. In this study, the authors found that the estimates of the efficacy of OPV increased in the case-exposure method and also they reported that the estimated vaccine efficacy to OPV for fully immunized children aged 12--23 months exceeded 90% in Bombay.
Alan Werzberger MD et al. (1992) highlighted the efficiency of a formalin inactivated hepatitis A Vaccine in the study “A Controlled Trial of a formalin- Inactivated Hepatitis A Vaccine in Healthy Children”. In this study, they conducted a double-blind, placebo-controlled trial in a Hasidic Jewish community in New York due to frequent outbreak of Hepatitis A. This study revealed that the vaccine against Hepatitis A prevents the clinical disease in children, but does not show whether the vaccine will prevent sub clinical infection. And they also suggested that the vaccine proved early protection against the disease for the people who live in recurrently affected community. Clemens et al. (1998) discussed the significant role of vaccine effectiveness trials for assessing the performance of a vaccine that helps in taking quick decisions about time to introduce new vaccines and keeping public health concern in developing countries, in the article “Evaluating New Vaccines for Developing Countries: Efficacy or Effectiveness?”. They insisted that the vaccine effectiveness trial offered realistic perception of vaccine under the ordinary conditions of public health programme and may help to avoid a speculative dispute about practical costs and benefits. Furthermore, they suggested of implementing randomized trials to measure the effectiveness for overcome the deficiencies of efficacy trials as well as the problem related to observational studies.

Elizabeth Halloran M et al. (1999) reviewed different measures of effect of vaccination and vaccination programs in the study “Design and Interpretation of Vaccine Field Studies”. This study considered various study designs such as randomized, double–blinded, placebo controlled phase III trials, or phase IV post-licensure studies or observational studies and their interpretation. The study highlighted that in designing and understanding vaccine studies, it is necessary to be
Specific about what the effect of interest is and about the assumptions underlying the interpretation of the results. Jefferson. T et al (2005) identified the randomized controlled trial, cohort and case-control studies and assessed the vaccination with any influenza vaccine given to people aged 65 years or older. They had done a systematic review in the topic “Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review”. In this study, they observed that the aims of the vaccination campaign are fulfilled and the effectiveness of vaccine in the community is modest. They suggested that an effort should be taken on achieving high vaccination coverage in long – term care facilities and the investment in the development of better vaccines than that available at present should be linked to better knowledge of the cause and pattern of the disease in a different community.

Daniel O. Scharfstein et al. (2006) published a paper “On estimation of vaccine efficacy using validation samples with selection bias”. In this study, they developed Frequentist and Bayesian approaches for analyzing missing binary outcomes and for estimating Vaccine efficacy in the presence of validation bias. They suggested Frequentist or Bayesian Sensitivity analysis approach provides a larger amount of information than from the fully Bayesian analysis and Frequentist Sensitivity analysis is more practicable for computation more feasible and applicable for large sample size. But these approaches required experts view about way of validating selection bias. They found that their approaches are appropriate to all studies with missing binary outcomes with categorical covariates and it provides a higher degree of vaccine efficacy estimate.

Nicole E. Basta et al. (2008) suggested four measures of Vaccine efficacy of Influenza vaccine instead of taking the single measure in the study “Estimating
Influenza Vaccine Efficacy from Challenge and Community-based Study Data”. The authors compared the three different vaccines - live influenza, inactivated and attenuated vaccine of community-based vaccine trials with four measures of vaccine efficacy. They are vaccine efficacy for susceptibility (VES), for infection-confirmed symptomatic illness, for infectiousness and for illness given infection. They also proposed the combined vaccine efficacy measure based on all four measures of vaccine efficacy. They identified live influenza vaccine and inactivated vaccine provided similar protection against laboratory-confirmed infection, live vaccine had a higher efficacy for illness given infection than inactivated vaccine, but the difference was not significant. Clarissa Valim et al. (2008) proposed a paper “Estimation of vaccine efficacy in a repeated measures study under heterogeneity of exposure or susceptibility to infection”. In this study, the authors suggested an estimator of Vaccine efficacy per exposure that accounts for heterogeneous susceptibility and exposure for a repeated measures study with binary outcomes. They compared the properties of this estimator with proportional hazards estimation under the heterogeneity of exposure and recommended that the repeated measures model provide a flexible and convenient method of handling heterogeneity in susceptibility and in the vaccine efficacy per exposure.

Pier Luigi Lopalco (2009) reviewed various epidemiological methods for assessing safety and efficacy of vaccines in the paper “Assessing Vaccines and Vaccination Programmes in the field”. He insisted that several aspects of vaccination trials that should be assessed in order to improve the overall quality of vaccination programmes. For the sake of implementation, he suggested that the quality of vaccine, epidemiological and technical tools adopted by a health care professional
and political commitment should be considered necessary. Michel T Osterholm et al. (2011) presented the systematic review and Meta analysis on the topic “Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis”. This study reviewed 31 eligible studies in which 17 were randomized controlled trials and 14 observational studies. The protection of Influenza vaccine seems low or absent in adults aged 65 years or more, and evidence shows that approximately 90% of all seasonal influenza-related mortality occurs in this age group. An Influenza vaccine with live attenuated influenza vaccine (LAIV) provides a consistently higher level of protection in children aged less than or equal to 7 years. The study suggested that the new vaccines with enhanced potency are required to diminish influenza-related morbidity and mortality.

Adam L. Cohen et al. (2012) suggested screening and case-control method to compare estimates of heptavalent pneumococcal conjugate vaccine (PCV7) effectiveness against invasive pneumococcal disease (IPD) in the study "An Assessment of the Screening Method to Evaluate Vaccine Effectiveness: The Case of 7-Valent Pneumococcal Conjugate Vaccine in the United States". PCV7 vaccine coverage in pneumococcal surveillance areas was estimated using the U.S. National Immunization Survey from 2001 to 2009 for children 19-35 months of age. The authors recognized that the screening method should only be used as a preliminary test and estimates of vaccine effectiveness estimates derived from the screening method may require following verification with more accurate and valid methods.
2.2 STATISTICAL METHODS IN EPIDEMIOLOGY FIELD AND VACCINATION TRIALS

Patrick Royston et al. (1999) suggested an alternative approach based on fractional polynomial instead of traditional approaches for the analysis of continuous variables in an article “The use of fractional polynomial to model continuous risk variables in epidemiology”. This paper considered two main problems, the first one is how to analyze continuous risk variables using categories or continuous functions? And the second one is how to develop the mathematical formula for the risk function? The authors concluded that a continuous parametric model predicts smoothly changes risk and fits the data sufficiently more conceivable than any cut-point based model in epidemiological studies. Aluisio JD Barros and Vania N Hirakata (2003) investigated the alternative models with robust variance to estimate the prevalence ratio in the paper “Alternatives for Logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio”. In this paper, the authors compared Mantel-Haenszel estimators with Cox Regression with constant time at risk, Poisson Regression and log-Binomial models. They mentioned that odds ratio could overestimate the prevalence ratio with frequent occurrence of the outcome in any study. In this study, they suggested that the log-Binomial, Cox and Poisson Regression models with adjusted variances provides better estimates than Logistic regression to analyze cross-sectional data with binary outcomes and they also suggested the prevalence ratio easier and understandable than odds ratio.

Louise-Anne McNutt et al.(2003)suggested adjusted odds ratio obtained from the Logistic regression model for estimating approximated relative risk, especially in
case of rare outcomes of interest in the research article "Estimating the Relative Risk in Cohort Studies and Clinical Trials of Common Outcomes". The authors also recommended log-Binomial model to estimate an adjusted relative risk like Logistic regression, but they also tried to point out the difference between the logistic model and the log-Binomial model and the link between the independent variables and the probability of the outcome. This study proposed an alternative statistical method for estimating an adjusted relative risk when the outcome is common. Flynn NM et al. (2005) conducted a double-blinded, randomized trial of a vaccine study of a recombinant Glycoprotein (RGP) 120 HIV vaccine to prevent HIV infection and published an article “Placebo-Controlled Phase 3 Trial of a Recombinant Glycoprotein 120 Vaccine to Prevent HIV-1 Infection”. A generalized-estimating-equation model was used to estimate the mean difference between the vaccine and placebo. Cox proportional hazards models were used to estimate whether vaccine efficacy differed by various attributes (age, sex, education, race and behavioral risk). The study identified that there were no significant differences in rates of antiretroviral-therapy initiation, or the genetic characteristics of the infecting HIV-1 strains between treatment arms and there was no overall protective effect. Jonathan A. C. Sterne et al. (2009) dealt with the significance of missing data in the analysis and attempted to find out risk of bias due to missing data in the article “Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls”. They classified the reasons of missing data into three categories: (1) missing completely at random (MCAR), (2) missing at random (MAR), and (3) missing not at random (MNAR). The authors introduced Multiple Imputation Method to resolve the uncertainty about missing data by creating a number of
plausible imputed datasets, using statistical methods to fit the model of interest to each of the imputed datasets and obtained results from each of them. This study recommended that multiple imputations had potential to improve the validity of medical research and to minimize the waste of resource caused by the missing data. Philip W. Kantoff et al. (2010) conducted Therapeutic Prostate specific Antigen (PSA) targeted proviral vaccines for cancer randomized controlled trial and evaluate the effect of treatment on progression free survival (PFS) and overall survival in the study “Overall Survival Analysis of a Phase II Randomized Controlled Trial of a Poxviral Based PSA Targeted Immunotherapy in Metastatic Castration Resistant Prostate Cancer”. The stratification is done in the ratio 2:1 (PROSTVAC : control). The time-event end points were analyzed using the stratified log rank test and stratified proportional hazard regression. The authors proposed that PROSTVAC immunotherapy was acceptable and responsible for a 44% reduction in the death rate.

2.3 VACCINATION TRIAL ON LEPROSY

Numerous studies have been developed in the estimation of vaccine efficacy using case-control study and prospective cohort study and these studies revealed different information. Various BCG against leprosy vaccination trail have been conducted and efficacy of BCG has been estimated in case-control and cohort studies.

Bechelli L. M et al. (1973) conducted a controlled BCG vaccine for the prevention of Leprosy in Burma and presented a paper after 6 years follow up examinations of the trail up to 1968 on the topic “BCG vaccination of children against leprosy: seven-year findings of the controlled WHO trial in Burma”. In this
trial, 28,220 numbers of children were included, among them 2,716 cases were identified. The study recommended that the nationwide BCG vaccination of children aged 0–4 years in areas of high risk of epidemic with the aim of preventing tuberculosis and also preventing leprosy. The study revealed that the incidence rate in BCG-vaccinated children 0-4 years of age at the time of intake was lower than that in children in the control group and BCG vaccination did not protect household contacts or children 5-14 years of age who were not exposed.

Kyaw Lwin et al. (1985) studied the protective effect of BCG vaccine in preventing leprosy among children in an area of high leprosy prevalence in Burma and published an article in the topic “BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma”. In this study, around 26,000 children aged 0-14 years were involved in the trial, among them one group of 13,066 children received BCG and another group of 13,176 considered as controls. The authors assessed the overall protective effect of BCG vaccine was 20% over the 4 year period and also found the protective effect vary with various characteristic such as the batch of vaccine, age, sex, and contact status of the children. And also, the study exposed that BCG provides only a very modest level of protection and that BCG vaccination is not likely to be an important solution for leprosy control.

Gupte M. D. et al. (1998) had conducted controlled, double-blind, randomized, prophylactic leprosy vaccine trial from 1991 to 1993 in Tamilnadu. They studied four vaccines (BCG, BCG+Killed, M. Leprae, M.w and ICRC) with normal saline placebo and reported in the paper “Comparative leprosy vaccine trial in South India”. Around 1,71,400 participants were administered vaccine in the study and two consecutive resurveys were conducted at regular interval. This study
facilitated to assess and compare the protective efficacy of four different vaccines against leprosy. And they have recommended ICRC vaccine and the combination vaccine (BCG+killed, M. Leprae) for further vaccination programmes in leprosy prevention.

Sreevatsa et al. (1998) assessed the quality of four vaccines (BCG, BCG+Killed, M. Leprae, M.w and ICRC) which were administered in the large leprosy vaccine trial through the quality control test and was published in an article “Quality Control Tests for Vaccines in Leprosy Vaccine Trial, Avadi”. The authors validated and showed that the vaccines were free from micro organisms and toxic materials and confirmed that the vaccines were safe for human use. They also added that the quality of vaccine preparation was satisfactory.

Tanja Jeaggi (2007) identified the factors influencing the epidemiological trends of leprosy prevalence and occurrence, in terms of, sex, age and the proportions of multibacillary, disability and child leprosy cases in the three trial cohorts in her treatise “Epidemiological Trends of Leprosy in the Context of Control and Care”. In this study, she assessed the mechanisms behind the prevalence and incidence trends of this disease. She also discussed about the information gathered from qualitative data and about the epidemiological trends of leprosy vaccination trial conducted in Tamilnadu, India. She indicated that the percentage of children among leprosy cases seemed to decrease due to the effect of the vaccines, integration of leprosy services into primary health care and close surveillance of child leprosy cases in the leprosy vaccination trial.
Vasna Joshua et al. (2008) suggested Bayesian method to fit the prevalence of leprosy in spatial clustering, in the research paper “A Bayesian approach to study the space, time variation of leprosy in an endemic area of Tamil Nadu, South India”. The authors recommended the Bayesian technique as it would give a better understanding about the variation of the disease prevalence of leprosy over space and time while the other statistical method failed to do so. They found that the estimated period effects showed decreases in the risk of leprosy which could be due to better nutrition, hygiene and increased awareness about the disease. By observing the effect of the Bayesian approach, they showed a strong pattern of clustering towards the North-Eastern region of the study area which was overcrowded and its people belonging to poor economic status.

Premanshu Bhushan et al. (2008) compared WHO classification, slit–skin smears (SSS) and demonstration of bacilli in biopsies (bacterial index of granuloma or BIG) in terms of identifying multibacillary cases in the article “Diagnosing multibacillary Leprosy: a comparative evaluation of diagnostic accuracy of slit–skin smears, bacterial index of granuloma and WHO operation classification”. They studied 150 patients, among them only 141 were evaluated using detailed statistical analysis. And they also suggested in their study that the bacterial index of granuloma was the most sensitive and effective of all the three methods in diagnosing leprosy.

Diana N. J. Lockwood et al. (2012) suggested a study design to identify predictors of reactions and nerve function impairment in leprosy in the paper “Comparing the Clinical and Histological Diagnosis of Leprosy and Leprosy Reactions in the INFIR Cohort of Indian Patients with Multibacillary Leprosy”. They enrolled 303 patients in the study, out of which 265 patients were found at risk
of developing Type 1 reaction (T1R) in their baseline biopsy. They estimated that the Sensitivity and Specificity of clinical diagnosis for T1R was 53.1% and 61.9%, respectively, for Borderline Tuberculoid (BT) patients and 61.1% and 71.0% for Borderline Lepromatous (BL) patients. The author suggested that increasing biopsy rates would help in the diagnosis of reactions.

Renate A Richarduset al. (2013) suggested a study to observe the effect of chemoprophylaxis with SDR and immunoprophylaxis with BCG on the clinical outcome as well as on host immune responses and gene expression status in contacts of newly diagnosed leprosy patients in the article “The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial”. In this article they recommend Combined chemoprophylaxis and immunoprophylaxis is potentially powerful tool to reduce the transmission of M.Leprae among contacts of leprosy patients. And also they added that the combine use of BCG and Rifampicin will be a powerful in control the transmission of Leprosy.

Annette Rid et al. (2014) suggested an ethical framework about under which circumstances placebo use is acceptable and unacceptable in vaccine trail; and also they recommended placebo use may be acceptable if a locally affordable vaccine had developed, estimating the efficacy of an existing vaccine, testing a new vaccine when an existing vaccine is considered inappropriate for local use and determining the local burden of disease in the article “Placebo use in vaccine trials: Recommendations of a WHO expert panel”.
The Objective of the study

The main objectives of this study are [1] identifying the appropriate models to estimate the vaccine efficacy with respect to different circumstances and intended to suggest some new techniques to improve the methodology in estimation of such studies. [2] To identify influencing factors (characteristics) for prevalence of disease using various approaches [3] suggesting suitable statistical models to predict the disease for the certain period after the vaccination programme.