THE USE OF PNEUMOCOCCAL VACCINE IN A TERTIARY CARE CENTRE IN INDIA

A Dissertation done towards partial fulfillment of the requirements of the Tamil Nadu Dr. M. G. R. Medical University, Chennai for the M.D. (Branch – I) (General Medicine) exams to be conducted in February/ March 2009.

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "**THE USE OF PNEUMOCOCCAL VACCINE IN A TERTIARY CARE CENTRE IN INDIA**" done towards partial fulfillment of the requirements of the **Tamil Nadu Dr. M. G. R. Medical University**, Chennai for the **M.D. (Branch – I) (General Medicine)** exams to be conducted in February/ March 2009, is the bonafide work of the candidate Dr. Surya Achamma Eapen, post graduate student in MD (General Medicine). It was carried out in the Department of Medicine, Christian Medical College, Vellore under my supervision and guidance.

Guide

Dr. Kurien Thomas
Professor
Department of Medicine Unit II
Christian Medical College & Hospital,
Vellore

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "**THE USE OF PNEUMOCOCCAL VACCINE IN A TERTIARY CARE CENTRE IN INDIA**" done towards partial fulfillment of the requirements of the **Tamil Nadu Dr. M. G. R. Medical University**, Chennai for the **M.D. (Branch – I) (General Medicine)** exams to be conducted in February/ March 2009, is the bonafide work of the candidate Dr. Surya Achamma Eapen, post graduate student in MD (General Medicine). It was carried out in the Department of Medicine, Christian Medical College, Vellore under my supervision and guidance.

Head of Department

Dr. Dilip Mathai
Professor and Head
Department of Medicine Unit
Christian Medical College & Hospital,
Vellore

ACKNOWLEDGEMENTS

This thesis would not have been possible without My Lord and Savior Jesus Christ.

I have to thank my family, especially my husband for all the support, encouragement and advice.

I would like to thank my Guide, Dr. Kurien Thomas for his advice, guidance and timely reminders towards the planning and execution of the thesis.

I would like to thank the patients and their relatives for kindly co-operating with me and providing me with the necessary information for my study.

I would like to thank Mrs. Visalakshi and Mr. Prasanna from the Department of Biostatistics for the help that was extended in the analysis of the data.

This thesis is dedicated to my parents without whose help I could not have come thus far.

TABLE OF CONTENTS

INTRODUCTION

Pneumonias are a major cause of morbidity and mortality among all ages of people. The leading cause for community acquired pneumonia requiring hospitalization in about 36% of the adult population is *Streptococcus pneumoniae.* This organism also causes other invasive and life threatening conditions such as bacterial meningitis and streptococcal bacteraemia. It is estimated that nearly 400,000 children under the age of 5 years and an equal number of adults, die of pneumonia each year in India.

Although young children have the highest rates of pneumococcal disease, elderly persons and adults with certain chronic illnesses are also at high risk for invasive pneumococcal diseases. Invasive pneumococcal disease has a mean mortality of about 10% among normal individuals and this increase within the susceptible population.

The increased burden of Pneumococcal disease emphasizes the need for preventive measures, namely vaccination. The efficacy of Pneumococcal vaccine in preventing invasive pneumococcal infections has been found to be about 75%.

There is very little data on the use of Pneumococcal vaccine in India. Since invasive pneumococcal infections remain a major killer, it becomes necessary to study the use of Pneumococcal vaccine, including vaccination coverage and protective efficacy among the susceptible Indian population.

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

1. To determine the protective efficacy of Pneumococcal vaccine in a cohort of susceptible population in the Medical OPD followed up for a period of six months to one year.

SECONDARY OBJECTIVES:

2. To determine the rate of Pneumococcal vaccination among adult subjects who visit the Medical OPD and fulfill the criteria for vaccination.
3. To describe the current prescribing practices among physicians in the Medical OPD.
4. To identify the determinants of non vaccination among patients presenting to the Medical OPD.

LITERATURE REVIEW

Introduction

Pneumococcal infections remain a major cause of morbidity and mortality worldwide in spite of the availability of vaccines (1). The major cause of community acquired pneumonia in adults is *Streptococcus pneumoniae* (pneumococcus) (2, 3). *Streptococcus pneumoniae* can result in conditions ranging from nasopharyngeal colonization to otitis media, and invasive diseases such as meningitis, sepsis, bacteraemia, or pneumonia. *S. pneumoniae* may account for 30% to 50% of all adult community acquired pneumonias (CAP) requiring hospital admission and may also be the most frequent cause of pneumonia in long term care institutions (4, 5). A meta-analysis of 122 reports of CAP between 1966 and 1995 showed that *S. pneumoniae* caused 66% of nearly 7,000 cases having an established etiology(6) .

Although young children have the highest rates of pneumococcal disease, elderly persons and adults with certain chronic illnesses are also at high risk for invasive pneumococcal disease, and in industrialized countries, they are much more likely to die of pneumococcal disease than are children(7). Bacterial pneumonia and influenza together are the fifth leading cause of death in the elderly (people 65 years old and older)(8). According to the 1997 ACIP statement, people aged 2–64 years who have chronic illnesses that place them at moderate to high risk for pneumococcal disease or complications of pneumococcal disease should receive pneumococcal polysaccharide vaccine. These people include those with chronic cardiovascular disease (e.g., coronary

artery disease, congestive heart failure or cardiomyopathies), chronic pulmonary disease (e.g., chronic obstructive pulmonary disease or emphysema, but not asthma), diabetes mellitus, alcoholism, chronic liver disease (e.g., cirrhosis), CSF leaks, or functional or anatomic asplenia (7).

Burden of pneumococcal disease

The reported annual incidence of pneumococcal infections worldwide is between 130 and 210 cases for every 100,000 inhabitants, but the rate is higher in elderly persons and in patients with a compromised immune system(9). Recent data suggest that the rate of CAP in the US is 18.2 cases per 1,000 person-years in persons aged 65 to 69 years, rises to 52.3 cases per 1,000 person-years in those aged 85 years and older, and in nursing home residents, the rates of CAP are estimated to be more than 300 cases per 1,000 person-years(10-12). The annual incidence of invasive infections due to *Streptococcus pneumoniae* in adults older than 64 years in Chile, in a follow up period of five years, has been reported to be 234/100,000(13).

The organism colonizes the upper respiratory tract in approximately 50% of children and 2.5 % of adults (14). It can cause a wide spectrum of illnesses: upper respiratory tract infections including otitis media and sinusitis; pneumonia and other lower respiratory tract infections; and disseminated invasive infections, including bacteraemia and meningitis (7). Pneumococci that are resistant to penicillin and to multiple agents are becoming increasingly common among patients in all age groups, which makes pneumococcal infections more difficult to treat(15). The emergence of antibiotic-resistant pneumococci has placed renewed emphasis on the importance of disease prevention.

Humans are the only reservoir for these bacteria, hence it is theoretically possible to eradicate pneumococci by sufficient vaccination, similar to the pox virus.

Invasive pneumococcal disease has a mean mortality of 10%, which may rise to >30% in risk groups (e.g. nursing home residents >65 years of age)(16). In Germany, the incidence of these invasive pneumococcal diseases is between 4.6/1,00,000/year for patients <65 years and 16.2/100 000/year for patients ≥65 years (17)

Pneumococcal bacteriology and antibiotic resistance

Streptococcus pneumoniae is a Gram-positive encapsulated bacterium. The bacterial polysaccharide capsule contributes to the overall virulence of the pathogen and protects the bacterium from phagocytosis. Uncapsulated pneumococci such as the laboratory reference strain R6 are considered to be non-pathogenic. Ninety-one different capsular types (i.e. serotypes) have been described so far. Serotypes that are assessed by cross-reacting antibodies are summarised in serogroups.

Increased pneumococcal resistance worldwide is mainly due to the spread of multi resistant clones of the pathogen(18).The current nomenclature of these clones is defined by the Pneumococcus Molecular Epidemiology Network and consists of the country of origin, the serotype (in superscript) and a consecutive number (e.g. Spain^{23F}-1 or England^{14}-9(19). Current data demonstrate that pneumococcal resistance has also become a problem in countries with traditionally low resistance rates, such as Germany. A German study, which included children and adolescents <16 years of age suffering from invasive pneumococcal infections, showed that almost 29% of the pneumococci isolated

were macrolide-resistant (20). Thus, the proportion of macrolide-resistant species has increased three-fold in just 7 years (1997, 8.7%; 2004, 29%). Macrolide-resistant strains are of particular interest because macrolide resistance is associated with clinical treatment failure(21). In contrast to penicillin resistance, which might be relevant in the treatment of pneumococcal pneumonia only at very high minimum inhibitory concentrations (MICs) (>4 mg/L)(22), a Canadian observational study identified 64 so-called 'breaking through bacteraemias' during macrolide treatment. MIC determination of these isolates revealed that even slightly elevated MICs of ≥1 mg/L may lead to treatment failure (21).

Seroprevalence of pneumococcal infections

Determination of the seroprevalence of naturally developing antibodies to a pathogen within a population has proved to be useful in providing data on the epidemiology of infection (23) . The bacterial species *Streptococcus pneumoniae* consists of 90 immunologically distinct serotypes, of which some possess distinct epidemiological properties. Certain serotypes are much more likely to be associated with nasopharyngeal colonisation than to cause invasive disease. Compared with transient or infrequent colonisers, serotypes carried at high rates by young children may rapidly elicit age-associated natural immunity to invasive disease. Other serotypes seem to be of disproportionate importance as causes of disease in very young infants, in older children, in immunocompromised individuals, or in elderly people. Some serotypes seem to be associated with particular disease syndromes, such as complicated pneumonias in children, or with higher rates of hospitalisation in children or mortality in adults, or are consistently responsible for outbreaks in certain populations(24).

In a study done from Kenya, the descriptive epidemiology of *Streptococcus pneumoniae* in nasal swabs of adults and children in the Kilifi district of Kenya was done. In the dry season, 127 strains of *S. pneumoniae* were isolated; 4 individuals were infected simultaneously with two serotypes. Two strains could not be typed and the remaining 125 strains expressed 36 capsular types. In the rainy season survey, 152 strains expressing 31 different serotypes, were isolated from 146 individuals; 6 individuals were infected simultaneously with two serotypes. Seventeen individuals carried the same serotype in the two studies, of whom sixteen were aged <5 years. These strains were of serotypes 19F, 6B, 6A, 23B, 9V, 18F and 15A. Overall, 40 different pneumococcal serotypes were identified in the two surveys (25).

The IBIS study was a prospective, hospital-based surveillance study in six large academic referral hospitals of the International Clinical Epidemiology Network (INCLEN) which was done to assess the seroprevalence of invasive pneumococcal disease in Asia. Children aged younger than 12 years with any of the following clinical syndromes: pneumonia with radiographic evidence or meeting WHO clinical criteria, clinically suspected meningitis or cerebrospinal fluid (CSF) suggestive of bacterial meningitis; and fever at least 39°C for 2 days or less, with suspected bacterial infection due to *S pneumoniae* were recruited. Adults with clinical or radiographic evidence of pneumonia, or CSF findings suggestive of bacterial meningitis were eligible for inclusion. 6025 biological samples were collected from 5538 patients recruited by clinical criteria(26).

The most common serotype was type 1, which has largely disappeared from many developed countries (27, 28), but accounts for about 25% of Indian invasive isolates.

Serotype 6, which is the most common serotype in developed countries, was the second most common in this study, causing only 11·5% of the invasive infections (28). The proportion of isolates comprising the most frequent ten serotypes did not differ between study centres, and serotype 1 was the most common in all regions in the study. The most common serotypes in adults aged more than 65 years were serotype 1, 7, 3, 6, 8, 12, 16, 4, 9 and 14 (29).

Substantial differences in serotypes involved with invasive disease were found in different age-groups. In young children, *S pneumonia* types 6 and 19 seemed to be more common. A report from Bangladesh showed a different pattern of invasive serotype distribution and serotype 6 was not isolated from young children(30). However, the Bangladesh study population consisted of only children less than 5 years and 91% were younger than 2 years. Serotype 1 infection increased with age in these patients. There were no significant differences in the distribution of serotypes across the 4 years of the study.

A one-year prospective surveillance study from in three health care centers in Chile included blood culture in infants with suspected invasive bacterial disease or with fever higher than 39°C (axillary temperature) without focus or with acute otitis media . Out of 4,369 infants studied, 58 cases of invasive bacterial diseases were identified, 37 (64%) due to *S. pneumoniae.* The main serotypes identified were 18C, 14 , 19A(31).

Data from the Canadian National Centre for Streptococcus indicate the proportion of invasive pneumococcal isolates with reduced penicillin susceptibility increased from 5.5% to 15.2% between 1992 and 2000(32). The Canadian Bacterial Surveillance

Network has documented a similar trend of decreasing susceptibility to penicillin and to other antibiotics among pneumococcal isolates recovered from invasive, respiratory and other sites, between 1988 and 2001(33).

Immune responses induced by *Streptococcus pneumoniae*

Besides phagocytosis and intracellular killing by alveolar macrophages and neutrophil granulocytes (innate immunity), acquired humoral immunity is an important part of the host defence against pneumococci. As in other bacterial infections eliciting humoral responses, such a response requires processing and presentation of bacterial antigen in secondary lymphoid tissues(34).

Immature dendritic cells process and present pneumococcal peptides along with MHC II complexes to naive $CD4^+$ T-cells in the presence of co-stimulatory molecules such as CD80 and CD86. Such peptide antigen presentation results in T-cell proliferation and expansion of effector T-cells. IgM secreted by B-cells aids B-cells to capture and internalize soluble antigen via immunoglobulin receptors, which in turn promotes their capacity to mount increased IgM responses .Moreover, in the presence of co-stimulatory molecules, B-cells are also able to present processed antigen complexed with MHC II molecules to T-cells(35). B-cells, which are usually stimulated by Th2 cells and cytokines (i.e. interleukin (IL)-4, IL-5 and IL-6), differentiate into IgG-secreting plasma cells. IgG plays an important role in opsonophagocytosis of and complement-induced cytotoxicity against pneumococci by professional phagocytes. Appropriately triggered B-cells also release IgA, which is deposited on mucosal surfaces to protect against pneumococcal colonization.

In summary, current concepts consider polysaccharides as T-cell-independent antigens. However, in a recent in vitro study Stephen et al. demonstrated that capsular polysaccharides of serotype 1, even without conjugated protein, can be presented by dendritic cells to $CD4^+$ cells (36). However, the meaning of these observations for man is not yet understood.

Pneumococcal vaccines

Introduction: The burden of pneumococcal disease in the world underlines the need for an effective vaccine for the same.An ideal vaccine should elicit protective immunity and generate memory cells, which respond to subsequent antigen exposure (37). Although pneumococcal diseases are frequent and vaccine development was started early, the development of an efficacious vaccine was not successful for a long time. The main reason was the low immunogenicity of polysaccharides, which are the target of opsonising antibodies (33).

Pneumococcal vaccines were used as early as 1911(38).The first pneumococcal polysaccharide vaccines to be licensed in the United States, 2 different 6-valent formulations, were available shortly after World War II, but interest was very low in these vaccines and both were withdrawn from the market(39). A 14-valent formulation was licensed in 1977, and in 1983, this vaccine was replaced by the 2 currently available 23-valent pneumococcal polysaccharide. Presently, two types of vaccines are currently in clinical use: polysaccharide vaccines and pneumococcal conjugate vaccines (33).

Polysaccharide vaccines: Polysaccharide vaccines have been available since the mid 1980s. These vaccines contain purified capsular polysaccharides from 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6b, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F). Polysaccharides primarily induce a B-cell-dependent immune response via release of immunoglobulin M (IgM)(40). Pneumococcal capsular polysaccharide antigens induce type-specific antibodies that enhance opsonization, phagocytosis, and killing of pneumococci by leukocytes and other phagocytic cells. After vaccination, an antigen-specific antibody response, indicated by a twofold or greater rise in serotype-specific antibody, develops within 2-3 weeks in greater than or equal to 80% of healthy young adults(41); however, immune responses may not be consistent among all 23 serotypes in the vaccine. The levels of antibodies that correlate with protection against pneumococcal disease have not been clearly defined.

Antibody responses also occur in the elderly and in patients who have alcoholic cirrhosis, COPD, and insulin-dependent diabetes mellitus (7); however, antibody concentrations and responses to individual antigens may be lower among such persons than among healthy young adults. Persons aged greater than or equal to 2 years with anatomic or functional asplenia (e.g., from splenectomy or sickle cell disease) generally respond to pneumococcal vaccination with antibody levels comparable with those observed in healthy persons of the same age(42).

Conjugate vaccines: The heptavalent pneumococcal conjugated vaccine (PCV-7) contains capsular polysaccharides from those pneumococci (4, 6B, 9V, 14, 18C, 19F and 23F) that are most frequently involved in paediatric infections. Capsular polysaccharides

of PCV-7 are conjugated to highly immunogenic cross-reactive material 197 (CRM_{197}), a non-toxic diphtheria toxoid protein. Employment of this pneumococcal vaccine is particularly successful in the vaccination of young children. Similar to *Haemophilus influenzae* type B conjugate vaccination, CRM_{197}-specific type 2 helper T (Th2) cells interact with B-cells that have bound and internalized the polysaccharide–CRM_{197} complex via polysaccharide-specific IgM and subsequently present the processed CRM_{197} protein along with MHC II to effector T-cells. This type of adaptive immune response is characterised by antibody isotype switching and the generation of memory B-cells.

PCV-7 was approved in the USA in 2000 and since then in several additional countries. The 23-valent polysaccharide vaccine is primarily designed for use in older children and adults who are at risk for pneumococcal disease. It is not licensed for use in children <2 years of age. In some countries it is recommended by the public health authorities for all adults at the age of 60 years or older.

Advantages and disadvantages of currently used Pneumococcal vaccines

PCV-7 elicits a mucosal immune responses in immunised hosts, most probably due to induction of IgA antibodies. Mucosal immunity enables asymptomatic carriers to eradicate colonising pneumococci of vaccine serotypes. Furthermore, PCV-7 is effective in preventing invasive disease progression of vaccine serotypes. A disadvantage of conjugate vaccines is their low coverage of pneumococcal serotypes, which, for example, would result in protection against just 50% of pneumococcal infections occurring in adults (17). In contrast to the aforementioned conjugate vaccines, polysaccharide

vaccines do not induce mucosal immunity and thus do not affect carrier rates(43) or herd immunity. In addition, the occurrence of upper and lower respiratory tract infections cannot be prevented by a previous pneumococcal polysaccharide-based vaccination, although less severe disease courses have been reported. However, a major advantage of such a vaccine is the large number of included pneumococcal serotypes, leading in theory to a vaccine coverage of approximately 80% of adult pneumococcal infections (17)

Protection with pneumococcal vaccine

In a trial from Spain, where 524 patients with diagnosed pneumococcal pneumonia were studied(44),it was shown that the portion of patients (11%) who received the 23-valent pneumococcal vaccine within 5 years before hospitalisation showed significantly less bacteraemia (15% vs. 35%) compared with non-vaccinees. Despite a less favourable prognosis due to higher mean age as well as a higher risk of pneumonia-induced death according to the Pneumonia Severity Index, vaccinees showed a quicker defervescence (1.7 days vs. 2.9 days) and could be released from the hospital faster (9.4 days vs. 11.3 days). Mortality of vaccinees was also much lower (1.6% vs. 6.1%) even if this difference did not reach statistical significance(45).

In a meta analysis done in 1999, it was found that vaccination with Pneumo-23 would reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% and systemic infection due to all pneumococci by 73%.(46)

A placebo-controlled, double-blind trial done from Eastern Gambia assessed the efficacy of a nine-valent pneumococcal conjugate vaccine in children. Children age 6-51 weeks

were randomly allocated three doses of either pneumococcal conjugate vaccine (n=8718) or placebo (8719), with intervals of at least 25 days between doses. Efficacy of the conjugate vaccine was 77% (95% confidence interval CI 51-90) against invasive pneumococcal disease caused by vaccine serotypes, 50% (95% confidence interval CI 21-69) against disease caused by all serotypes, and 15% (95% confidence interval CI 7-21) against all-cause admissions. An efficacy of 16% (95% confidence interval CI 3-28) against mortality was also found.(47)

The benefit of pneumococcal polysaccharide vaccines for public health has also been studied. Between 1995 and 1998, among all Stockholm residents >65 years of age (n = 259 627), 1, 00,242 individuals were vaccinated against pneumococcal and influenza infections. Subsequently, hospitalizations occurring during December 1998 to May 1999 were recorded. Expectedly, reduced pneumonia- and influenza-associated diseases were observed in the immunized group. More specifically, overall mortality was lower by 57% (95% confidence interval 55–60%) in the vaccinee group compared with non-vaccinees (15.1 vs. 34.7 deaths per 1000 residents; $P < 0.0001$)(48).

Groups at risk for pneumococcal disease

Elderly: Pneumonia in elderly patients is often caused by micro aspiration of upper respiratory tract secretions colonized by *S. pneumoniae*, especially in those with an alteration in local defense mechanisms. Elderly individuals often have medical histories, underlying conditions, or chronic diseases that increase their risk of pneumonia, such as chronic cardiac and pulmonary conditions, diabetes mellitus, alcoholism with liver failure, dementia, cerebrovascular diseases, and smoking habits (49, 50). Pneumococcal

diseases are traditionally community-acquired pathologies. Long-term care facilities, or nursing homes, are unique among community settings, providing an environment rich in susceptible hosts and ideally suited for spread of respiratory diseases.

The EVAN-65 study which was a long prospective study to evaluate the controversial effectiveness of the 23-valent PPV in older adults revealed that pneumococcal vaccination was associated with significant reductions in the risk of hospitalization for pneumonia (hazard ratio HR 0.74; 95% confidence interval CI, 0.59–0.92) and in the overall pneumonia rate HR, 0.79; 95% CI, 0.64–0.98). The incidence of invasive pneumococcal disease was low (64 cases per 100,000 person-years), and a considerable protective effect against invasive pneumococcal disease did not attain statistical significance (hazard ratio HR, 0.60; 95% confidence interval CI, 0.22–1.65). However, the vaccine showed a significant effectiveness of 45% to prevent pneumococcal pneumonia (hazard ratio HR, 0.55; 95% confidence interval CI, 0.34–0.88). Finally, vaccination was associated with a significant 59% reduction in the risk of death due to pneumonia among vaccinated subjects (hazard ratio HR, 0.41; 95% confidence interval CI, 0.23–0.72)(51).

However, in a prospective cohort study conducted among patients above the age of 65 in Tarragona, Spain , it was shown that pneumococcal vaccination did not alter the risk of hospitalisation from pneumonia (hazard ratio HR: 0.80; 95% confidence interval (CI): 0.50–1.28) or overall pneumonia (hazard ratio HR: 0.86; 95% confidence interval CI: 0.56– 1.31), but the vaccine was associated with considerable reductions of death risk from pneumonia (hazard ratio HR: 0.28; 95% confidence interval CI: 0.09–0.83)(52).

A systematic review of all studies which evaluated pneumococcal vaccination in individuals 55 years and older showed no significant efficacy of the pneumococcal polysaccharide vaccine in subgroups of older adults (patients above the age of 65), hospitalized individuals more than 55 years of age or with risk factors like Diabetes Mellitus, Chronic obstructive pulmonary disease and chronic heart failure and patients in long term care facilities. These subgroup studies lacked power to show significant differences. However, observational studies have repeatedly demonstrate efficacy in older adults, and the vaccine has been demonstrated to be cost-effective and safe(53).

The efficacy of pneumococcal polysaccharide vaccine in selected populations at risk for serious pneumococcal infection for whom vaccination is currently recommended was evaluated by the Centers for Disease Control and Prevention between May 1978 and April 1992. Efficacy for immunocompetent persons older than 65 years was 75% (95% CI, 57% to 85%)(54).

The majority of systematic reviews did not find a significant protective effect of PPV(Polysaccharide pneumococcal vaccine) against noninvasive disease or overall pneumonia in the elderly. It is possible that PPV could not avoid the infection due to Pneumococcus in many elderly subjects. However, PPV may decrease the severity of pneumococcal infection by preventing invasion of the bloodstream and the incidence of the bacteraemia, it may also decrease mortality.

Immunocompromised and people with chronic diseases: Immunocompromised people and people with certain chronic illness are at increased risk for invasive pneumococcal disease or for severe sequelae from their infections. Adults at increased risk include those

who are generally immunocompetent but who have chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease {COPD} or emphysema), or chronic liver diseases (e.g., cirrhosis). Diabetes mellitus often is associated with cardiovascular or renal dysfunction, which increases the risk for severe pneumococcal illness (7). The incidence of pneumococcal infection is increased for persons who have liver disease as a result of alcohol abuse(7) .Persons with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy) are at highest risk for pneumococcal infection, because this condition leads to reduced clearance of encapsulated bacteria from the bloodstream (7). Asthma has not been associated with an increased risk for pneumococcal disease, unless it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids.

As per the Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network, people with chronic diseases namely chronic cardiovascular diseases, chronic pulmonary diseases, chronic liver diseases, diabetes, alcohol abuse, asplenia, immunosuppressive conditions, organ or bone marrow transplantation, chronic renal failure or nephrotic syndrome, and cerebrospinal fluid leakage were twice as likely as others to die if they develop invasive pneumococcal disease(55).

The efficacy of pneumococcal polysaccharide vaccine in selected populations at risk for serious pneumococcal infection for whom vaccination is currently recommended was evaluated by the Centers for Disease Control and Prevention between May 1978 and April 1992. Overall efficacy for preventing infection caused by serotypes included in the vaccine was 57% (95% confidence interval CI, 45% to 66%). Efficacy among persons

with diabetes mellitus was 84% (95% confidence interval CI, 50% to 95%); with coronary vascular disease, 73% (95% confidence interval CI, 23% to 90%); with congestive heart failure, 69% (95% confidence interval CI, 17% to 88%); with chronic pulmonary diseases, 65% (95% confidence interval CI, 26% to 83%); and with anatomic asplenia, 77% (95% confidence interval CI, 14% to 95%)(54). However, efficacy was not documented for patients with alcoholism or cirrhosis, sickle cell disease, chronic renal failure, lymphoma, leukemia, or multiple myeloma, although sample sizes were small for these groups. In a study from San Francisco that reviewed cases of invasive pneumococcal disease that occurred during 1994–1997, the rate of invasive pneumococcal disease in people with AIDS was 46 times higher than was the rate among people without known HIV infection (53). A trial which included follow up of HIV-infected Ugandan adults showed a survival advantage favouring vaccination (HR 0.84; CI 0.7-1.0) (56)

In a study from San Francisco that reviewed cases of invasive pneumococcal disease that occurred during 1994–1997, the rate of invasive pneumococcal disease in people with AIDS was 46 times higher than was the rate among people without known HIV infection(57).

In a study done from Chicago which was done to evaluate the impact of pneumococcal vaccination on rates of pneumonia-related hospitalizations in patients with chronic obstructive pulmonary disease (COPD) relative to patients without , it was found that COPD patients with a history of pneumococcal vaccination had decreased rates of pneumococcal pneumonia hospitalizations after vaccination(58).

Smokers: Smoking is not currently an indication for pneumococcal polysaccharide vaccine, but smoking has recently been identified as another major risk factor for invasive pneumococcal disease in adults. In population-based surveillance in Texas, smokers who were 18–64 years old had 2.6 times the risk for invasive pneumococcal disease as nonsmokers who were the same age, and 31% of disease in the patients in this age group was attributable to smoking(59). In a recent risk-factor study of immunocompetent adults aged 18–64 years, 51% of disease in this population was attributed to smoking, and smoking conferred a greater risk of invasive pneumococcal disease than that of any other characteristic studied (60). When researchers adjusted for other factors, people with invasive pneumococcal infection were 4.1 times more likely to be cigarette smokers than was the control group. The association increased with the number of cigarettes smoked and the number of years that the patient had smoked. Inspite of evidence of increased risk of pneumococcal infections in the smokers, smoking is not a risk factor identified under the ACIP guidelines.

Patients in long term care facilities: Pneumococcal disease is a major problem in long-term care facilities, and current vaccine recommendations suggest that institutionalized adults should receive polysaccharide vaccine. Not only are long-term care facility residents at high risk for sporadic pneumococcal disease as a result of their advanced age or the presence of chronic illnesses, but long-term care facilities also provide an optimal setting for pneumococcal outbreaks. Several outbreaks of infection have been reported, including one in which the outbreak strain was multidrug resistant (61-64). Low vaccine coverage may facilitate institutional outbreaks of pneumococcal disease; at the time of these reported outbreaks, approximately 10% of residents in the facilities had received

pneumococcal polysaccharide vaccine. Outbreaks of pneumococcal disease are rare outside of institutional settings.

Certain ethnic groups: There are marked differences in risk for some racial and ethnic groups. The rate of invasive pneumococcal disease in African-American persons aged 35–49 years exceeds that for white persons aged ≥ 65 years and African Americans at all ages have at least twice the risk of invasive pneumococcal disease as white persons in the United States(55, 59, 65-67). Rates of invasive pneumococcal infection are also higher among Alaska Natives(68)and certain other American Indian groups(69). The reasons for these differences in risk of invasive disease are not well defined. Differences in the prevalence of chronic diseases, such as HIV infection, AIDS, or diabetes, may contribute to the differences in risk between racial and ethnic groups(69, 70). However, studies that controlled for underlying diseases have still found higher risk of infection for African American persons than for persons of white race(65, 70). Although ACIP recommends that Alaska Natives and American Indians of all ages should receive pneumococcal polysaccharide vaccine because of high risk for invasive infection, current recommendations do not include African-American adults aged < 65 years without underlying illnesses.

Current recommendations for pneumococcal vaccination(7)

The vaccine is both cost effective and protective against invasive pneumococcal infection when administered to immunocompetent persons aged greater than or equal to 2 years or immunocompromised persons. Therefore, all persons in the following categories should receive the 23-valent pneumococcal polysaccharide vaccine, namely

1. Persons aged greater than or equal to 65 years.

2. Persons aged 2-64 years who have chronic illnesses, such as chronic cardiovascular disease (e.g., congestive heart failure {CHF} or cardiomyopathies), chronic pulmonary disease (e.g., COPD or emphysema, but not asthma), diabetes mellitus, alcoholism, chronic liver disease (cirrhosis), or CSF leaks.

3. Persons Aged 2-64 Years who have functional or anatomic asplenia

4. Persons Aged 2-64 Years who are living in special environments or social settings, namely Alaskan Natives and certain American Indian populations and residents of nursing homes and other long-term-care facilities.

5. Immunocompromised persons, such as persons with HIV infection, leukemia, lymphoma, Hodgkins disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation); and persons receiving immunosuppressive chemotherapy, including long-term systemic corticosteroids.

Coverage with pneumococcal vaccine:The present scenario

Scene in the developed countries: In 2004, the overall proportion of respondents aged ≥65 years reporting ever having received pneumococcal vaccine was 63.4% (CI = 62.7%--64.1%) in USA according to the National Health Interview Survey. Vaccination coverage ranged from 32.7% to 71.6%, with a median of 64.6%. In 2005, the overall proportion of respondents aged ≥65 years reporting ever having received pneumococcal

vaccine was 63.7% (CI = 63.1%--64.4%). Vaccination coverage ranged from 28.3% to 71.7%, with a median of 65.7%.Pneumococcal vaccination coverage increased by 32% (from 42.6% to 56.3%) among persons aged ≥65 years from 1997 to 2005, but coverage has remained nearly unchanged since 2002 (56.2%)(71).

In a descriptive study to assess the determinants of adult vaccination in inner city centres of USA, it was found that the rate of pneumococcal vaccination was 45% by self-report, 55% by medical record review. The rate of vaccination was 69% for patients 65 years old and older, 32% for patients 50–64 years; they did not differ by race (72). The differences in pneumococcal vaccination rates between younger and older adults is expected, as the recommendation for those younger than age 65 years is to vaccinate only those with high risk conditions such as chronic cardiac, pulmonary, liver or kidney disease.

In a study undertaken at two Victorian teaching hospitals to assess the coverage of influenza and pneumococcal vaccination among those aged above 65, it was found that pneumococcal vaccine coverage was 52.6 per cent (95% confidence interval CI 50.4-54.8) as opposed to influenza vaccine coverage which was 70.9 per cent (95% confidence interval CI 68.9-72.9). This highlights the need for greater awareness of pneumococcal vaccine among practitioners and for systematic recording of vaccination status (73).

Barriers to achieving high pneumococcal vaccination levels among adults include a) missed opportunities to vaccinate adults during contacts with health-care providers in offices, outpatient clinics, and hospitals; b) lack of vaccine delivery systems in the public and private sectors that can reach adults in different settings (e.g., health-care, workplace, and college or university settings); c) patient and provider fears concerning adverse

events following vaccination; and d) lack of awareness among both patients and providers of the seriousness of pneumococcal disease and benefits of pneumococcal vaccination(7). As pneumococcal vaccine effectively reduces the incidence of bacteraemia, the use of vaccine must be increased in accordance with recommendations.

Scene in Asia: Published data on the extent of the pneumococcal infections is grossly lacking for developing countries. About 36% of aetiology proven community acquired pneumonia in India is assumed to be due to Pneumococcus(74). In a study from Shimla, out of 70 patients with community acquired pneumonia, the aetiology was obtained in 53 (75.6%) patients. Out of these, 19 (35.8%) was due to *Streptococcus pneumonia.* Studies on acute respiratory infections in children in most of Asia have also highlighted the importance of *S. pneumoniae* as a common paediatric pathogen(75).

It is estimated that 410,000 children under the age of 5 years and an equal number of adults die of pneumonia each year in India. An editorial from the Indian Academy of Paediatrics showed a striking graphic that an estimated 25% of all child deaths in India are due to pneumonia(76). The fact that this high a burden of pneumonia has remained undiminished in India in spite of economic growth and decline in child mortality due to other diseases is a reminder of the importance of tackling pneumonia head on with dedicated resources. In this setting, the role of pneumococal vaccine to reduce the morbidity and mortality due to pneumonia in children cannot be undermined.

There are no studies which have evaluated the protective effect of pneumococcal vaccination among the susceptible adult population in India. Much work needs to be done

in this respect as invasive pneumococcal infections remain a leading killer among both children and adults on the Indian subcontinent.

MATERIALS AND METHODS

DESIGN:

A nested case control design to determine the protective efficacy of pneumococcal vaccine among the susceptible adult population presenting to the Medical OPD.

SUBJECTS:

Inclusion criteria

1) All adults above the age of 60 years at the time of recruitment
2) Adults between 18 and 59 years with any of the following co morbidities
    i. Chronic pulmonary condition like Chronic Obstructive Pulmonary Disease, Interstitial Lung Disease or Bronchiectasis
    ii. Chronic cardiac condition like Coronary Artery Disease or Congestive Cardiac Failure
    iii. Chronic Renal Failure
    iv. Chronic Liver Disease
    v. Immunocompromised conditions like Human Immuno Virus Infections or chronic steroid abuse
    vi. Haematological conditions like Leukaemia, Lymphoma or Multiple Myeloma
    vii. Diabetes Mellitus

LOCATION:

The study was conducted in the Out patient Clinics of the 3 Medical Units, Christian Medical College and Hospital, Vellore.

DURATION:

The study was conducted between a period of time from 01.07.2007 till 31.07.2008.

METHODOLOGY:

Assessment of Protective Efficacy of 23 valent Pneumococcal Polysaccharide Vaccine:

Adults presenting to the Medical OPD who fulfilled the inclusion criteria were chosen for the study. The subjects were chosen between July 2007 and January 2008.

The subjects thus chosen were interviewed and were educated about Pneumococcal vaccination and its benefits.

The subjects' response and willingness for vaccination was documented.

Those who were willing to receive the vaccination were given Inj. Pneumo-23 0.5 ml subcutaneously after obtaining informed consent.

All recruited subjects were followed up for a period of six months to one year. The follow up period lasted till the end of July 2008.

Subjects were followed up for –

i. Development of respiratory symptoms suggestive of pneumonia- fever, cough, yellow sputum

ii. Exacerbation of COPD

iii. Development of symptoms of meningitis- fever, headache, vomiting

iv. Episodes of hospitalization for any of the above mentioned causes

Follow up of subjects:

All recruited subjects were contacted through post/telephone every month and were encouraged to come to Hospital in case of any symptoms. They could also contact the examiner in case they developed symptoms.

They were also given a symptom diary where they were to record all their symptoms even if a Hospital visit was not warranted. This was assessed at the time of routine visits.

Selection of cases and controls:

At the end of the study period, the subjects with outcomes were taken as cases and all those without outcomes (who did not have any complaints) were taken as controls (Nested Case Control Study).

They were then analyzed as to whether they had received the vaccination. The odds of cases having been vaccinated was calculated and the protective efficacy of the vaccine was obtained.

Assessment of vaccination status of eligible subjects attending CMC Hospital, Vellore:

A survey was conducted among the subjects visiting Medical OPD for a period of one week (2 OPD days of each unit) prior to recruitment of patients. The subjects were included according to the inclusion criteria and the number of eligible subjects visiting Medical OPD in one week was determined.

The number of subjects who were prescribed and who had bought the 23 valent Pneumococcal vaccine from the Medical OPD in a span of 1 year prior to the study period was obtained from computerized treatment records kept in the Pharmacy .

From this data, the rate of vaccination among eligible adults attending Medical OPD was calculated for one year before the study period as follows:

$$\frac{\text{number of people vaccinated in1 year}}{52(\text{Number of eligible subjects visiting OPD in one week})}$$

Assessment of causes of non vaccination from the subjects' perspective:

The subjects' reasons for unwillingness for receiving the vaccine were documented and the reasons for non vaccination from the subjects' perspective were described.

Assessment of reasons for poor prescribing practices by Medical Consultants:

A questionnaire was administered to all available practicing physicians in Medical OPD and the pattern of prescription of the vaccine and causes for non vaccination were obtained and described.

STATISTICAL ANALYSIS:

Sample size estimation:

Assuming that the adults who receive pneumococcal vaccination are 70%(O.R 0.3) less likely to have pneumococcal infections, the required sample size would be 80 cases and 80 controls with 80% power, 5 % alpha level of significance and 30% prevalence of vaccination in the general population.

Analysis:

Statistical analysis was done using the SPSS Software version 15.0. Univariate analysis was done using the chi square test or fishers exact test (cell size<5) for discrete variables. Subsequently, the distribution of time to outcome between the vaccinated and non vaccinated groups was described by a log rank test.

Odds Ratio was calculated for individual outcomes which included-

a) Respiratory symptoms
b) Acute exacerbation of COPD
c) Hospitalisation
d) Death

Odds Ratio was also calculated for a composite outcome which included all the above outcomes to determine an overall efficacy rate for the vaccine.

	vaccinated	Non vaccinated
outcome	a	b
No outcome	c	d

Odds Ratio= Odds in favour of vaccination among cases (those with outcome)
Odds in favour of vaccination among the controls (those without outcomes)

$$= \frac{a/b}{c/d} = \frac{ad}{bc}$$

Vaccine efficacy was calculated as 1- Odds Ratio x 100%.

RESULTS

BASELINE CHARACTERISTICS:

160 patients were recruited in the study period between 01.07.2007 and 31.07.2008. All the patients fulfilled the inclusion criteria for receiving the 23 valent pneumococcal vaccine.

83 out of 160 (51.9%) [CI (44.1-59.6%)] patients received the vaccine whereas 77 out of 160 (48.1%) [CI (40.4-55.9%)] patients did not receive the vaccine.

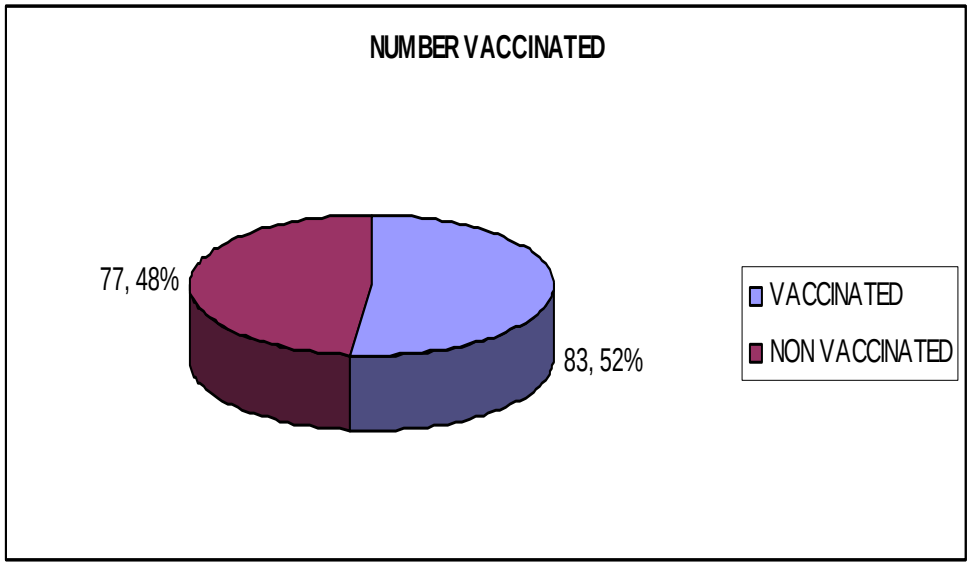


Fig.1

Out of a total of 160 patients, 94 (59%) were males and 66 (41%) were females.

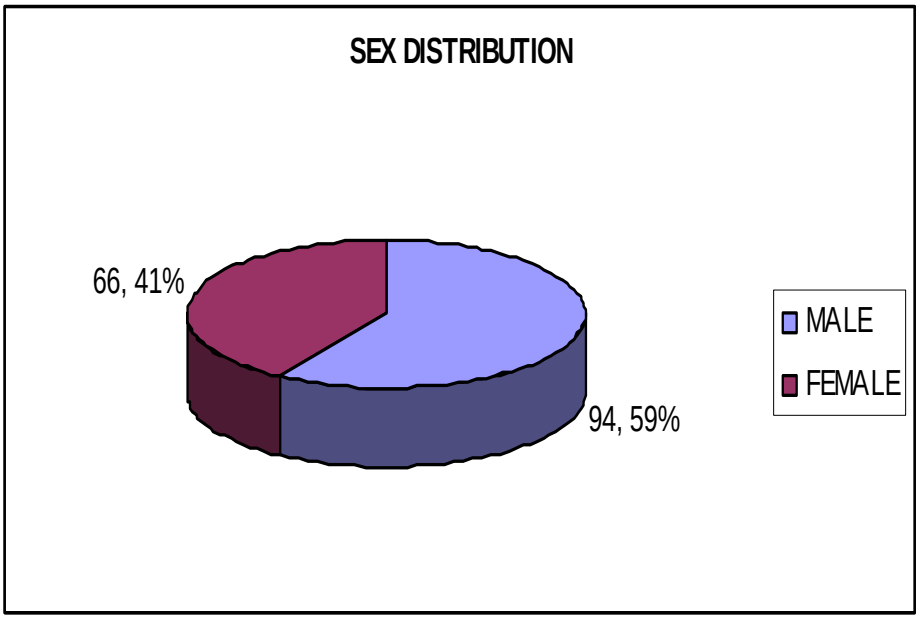


Fig.2

The minimum age of recruitment was 36 years whereas the maximum age was 88 years.

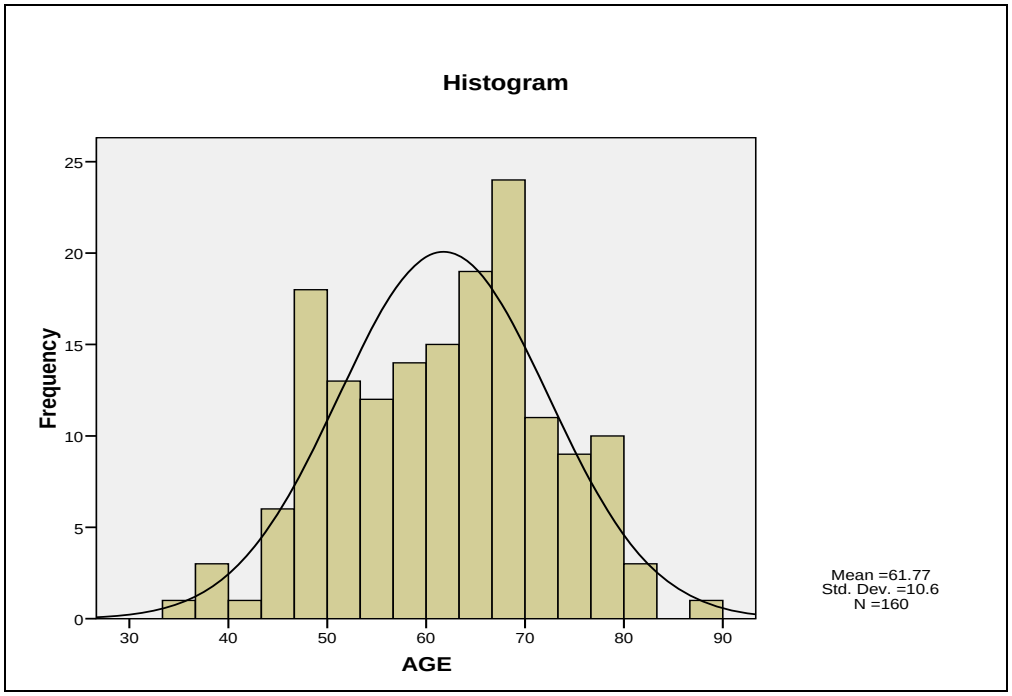
The mean age was 61.8 years (SD 10.6) with a median age of 63 years.

AGE DISTRIBUTION

Age	
Mean	61.8
Median	63.0
Std. deviation	10.6
Range	52
Maximum	88
Minimum	36

Table.1

AGE DISTRIBUTION



BASELINE CHARACTERISTICS

	VACCINATED	NON VACCINATED
AGE (years)	63.43±1.074	59.97±1.277
SEX M:F	53: 30	41: 36
RISK FACTORS (No)		
Age > 60 Years	55	35
COPD	30	26
Cardiac disease	11	8
Diabetes Mellitus	61	52
Chronic renal failure	0	4

Table.2

LOST TO FOLLOW UP:

At the end of the study period, 136 (85%) [CI (79.5-90.5%)] patients had been followed up whereas 24 (15%) [CI (10 -20.5%)] patients were lost to follow-up (ie. could not be followed up even once). 18 out of 24 were in the non vaccinated group whereas 6 out of 24 were in the vaccinated group.

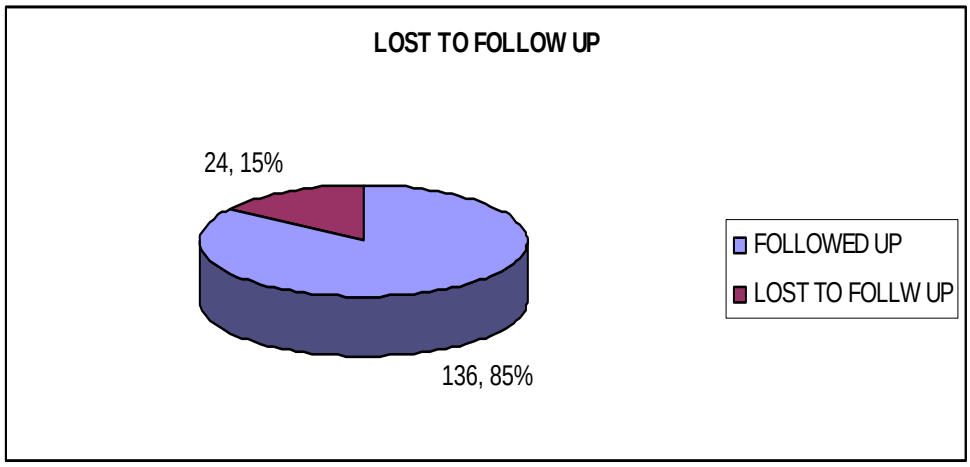


Fig.4

RATE OF VACCINATION:

No. of patients fulfilling the inclusion criteria for vaccination, visiting Medical OPD in one week	829
No of patients fulfilling the inclusion criteria for vaccination visiting Medical OPD in one year	829 x 52 = 43108
No. of vaccinated patients in the previous one year as per records	444
Percentage of eligible patients who were vaccinated	444/43108 x 100 = 1.03%

Table.3

Thus 1.03% [CI(0.93-1.13%)] of the eligible population were vaccinated from Medicine OPD prior to the study.

VACCINATION STATUS AND DEVELOPMENT OF COMPOSITE OUTCOME:

At the end of the study period, there were 53 patients who developed an outcome (any one of the following- respiratory symptoms, exacerbation of COPD, hospitalization, death) and 83 patients who did not develop an outcome. Out of the 53 who developed an outcome, 39 were in the non vaccinated group whereas 14 were in the vaccinated group.

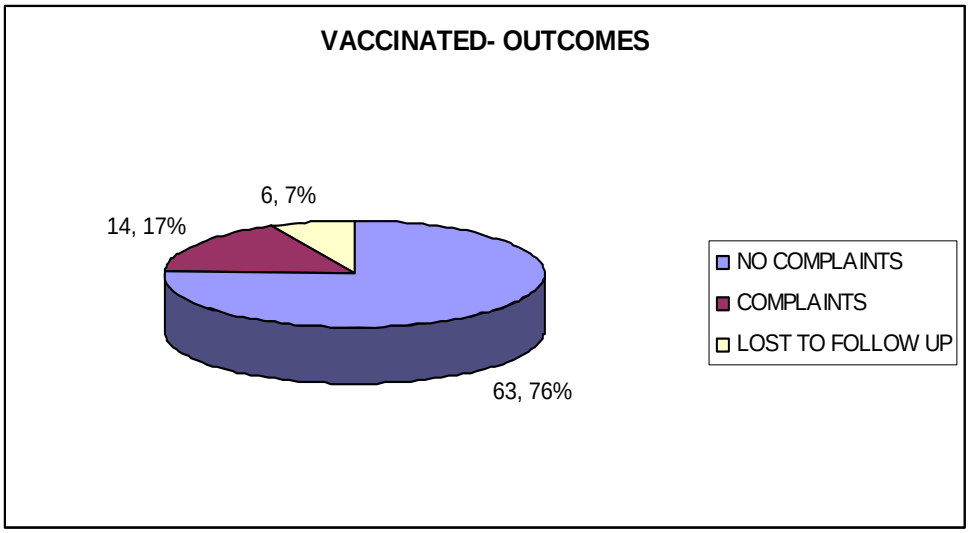


Fig.5

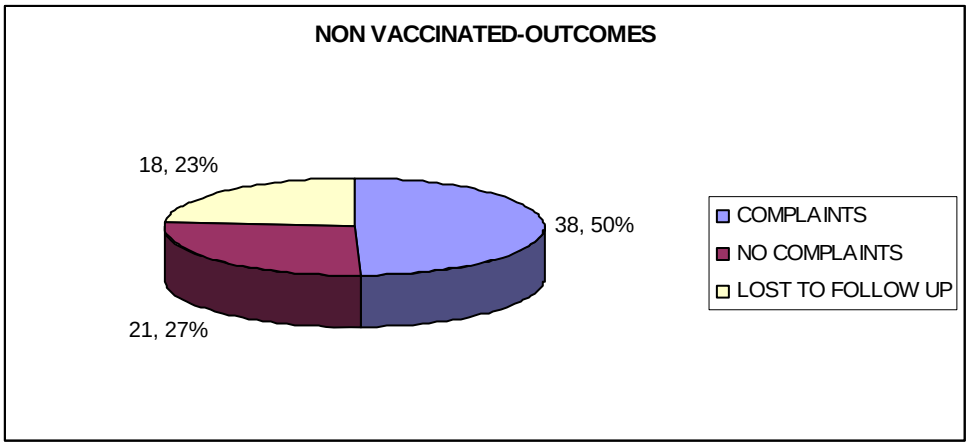


Fig.6

VACCINATION STATUS AND COMPOSITE OUTCOME

	OUTCOMES	NO OUTCOMES	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	14 (18.2%)	63 (81.8%)	77	0.11 95% CI (0.05-0.25)	< 0.001
NON VACCINATED	39 (66.1%)	20 (33.9%)	59		

Table.4

Odds Ratio: (14x20)/(63x39) = 0.11. [CI (0.05-0.25)]

Patients who had outcomes were 89% less likely to be vaccinated than the patients who did not have outcomes. (p value <0.001)

VACCINATION STATUS AND DEVELOPMENT OF RESPIRATORY SYMPTOMS:

Among the 160 patients who were vaccinated, 38 developed symptoms of fever and cough with yellow sputum. Out of these 38 patients, 29 were in the non vaccinated group whereas 9 were in the vaccinated group.

VACCINATION STATUS AND RESPIRATORY SYMPTOMS

	SYMPTOMS	NO SYMPTOMS	TOTAL	ODDS RATIO	P - VALUE
VACCINATED	9 (11.7%)	68 (88.3%)	77	0.14 95%CI (0.06-0.32)	<0.001
NON VACCINATED	29 (49.1%)	30 (50.9%)	59		

Table.5

Odds Ratio: (30x9)/ (29x68) = 0.14. [CI (0.06-0.32)]

Patients who developed symptoms suggestive of pneumonia, ie fever and cough with yellow sputum were 86% less likely to be vaccinated as compared to the patients who did not develop these symptoms. (p value <0.001)

VACCINATION STATUS AND DEVELOPMENT OF COPD EXACERBATION:

9 patients out of the 160 patients who were recruited developed an acute exacerbation of COPD. Out of these 9 patients, 2 patients belonged to the vaccinated group and 7 patients belonged to the non vaccinated group.

VACCINATION STATUS AND COPD EXACERBATION

	COPD EXACERBATION	NO EXACERBATION	TOTAL	ODDS RATIO	PVALUE
VACCINATED	2 (2.6%)	75(97.4%)	77	0.19 95%CI (0.04-0.99)	0.04
NON VACCINATED	7(11.9%)	52(88.1%)	59		

Table.6

Odds Ratio: (52x2)/ (7x75) = 0.19. [CI (0.04-0.99)]

Patients who developed COPD exacerbations were 81% less likely to be vaccinated as compared to those who did not develop an exacerbation. (p value = 0.04)

VACCINATION STATUS AND HOSPITALISATION:

There were 7 patients who required hospitalization for the various outcomes over a period of one year. Out of these 7 patients, 6 belonged to the non vaccinated group whereas 1 patient had been vaccinated.

VACCINATION STATUS AND HOSPITALISATION

	HOSPITALIZED	NOT HOSPITALIZED	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	1(1.3%)	76(98.7%)	77	0.12 95%CI (0.01-0.99)	0.04
NON VACCINATED	6(10.2%)	53(89.8%)	59		

Table.7

Odds Ratio: (53x1)/ (76x6) = 0.12. [CI (0.01-0.99)]

Patients who were hospitalized were 88% less likely to be vaccinated as compared to those who were not hospitalized. (p value = 0.04)

VACCINATION STATUS AND MORTALITY:

There were 6 deaths in a period of one year, 3 were in the vaccinated group and 3 in the non vaccinated group. There was no significant association between vaccination status and occurrence of death. (p value = 0.93)

VACCINATION STATUS AND MORTALITY

	DEATH	NO DEATH	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	3(3.9%)	74(96.1%)	77	0.76 95% CI (0.15-3.89)	0.93
NON VACCINATED	3(5.1%)	56(94.9%)	59		

Table.8

Odds Ratio: (56x3)/ (74x3) = 0.76. [CI (0.15-3.89)

SENSITIVITY ANALYSIS:

Given the fact that there were more number of patients lost to follow up in the non vaccinated group, an analysis of the worst case scenario was also done in which all patients who were lost to follow up were considered to have no symptoms.

VACCINATION STATUS AND DEVELOPMENT OF COMPOSITE OUTCOME:

	OUTCOMES	NO OUTCOMES	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	14(16.9%)	69(83.1%)	83	0.2 95%CI(0.09-0.40)	<0.001
NON VACCINATED	39(50.6%)	38(49.4%)	77		

Table.9

Odds Ratio: (14x38)/ (39x69) = 0.2. [CI (0.09-0.40)]

Assuming that all patients who were lost to follow up did not develop outcomes, the odds ratio of patients who were vaccinated developing outcomes was 0.2. Thus, the patients who were vaccinated were 80% less likely to develop an outcome. (p value < 0.001)

VACCINATION STATUS AND DEVELOPMENT OF RESPIRATORY SYMPTOMS:

	SYMPTOMS	NO SYMPTOMS	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	9(10.8%)	74(89.2%)	83	0.2 95%CI(0.09-0.46)	< 0.001
NON VACCINATED	29(37.7%)	48(62.3%)	77		

Table.10

Odds Ratio: (9x48)/ (74x29) = 0.2. [CI (0.09-0.46)]

Assuming that all patients who were lost to follow up did not develop respiratory symptoms, the odds ratio of patients who were vaccinated developing symptoms of pneumonia was 0.2, that is patients who were vaccinated were 80% less likely to develop symptoms of fever and cough with yellow sputum. (p value < 0.001)

VACCINATION STATUS AND DEVELOPMENT OF COPD EXACERBATION:

	COPD EXACERBATION	NO COPD EXACERBATION	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	2(2.4%)	81(97.4%)	83	0.25 95%CI(0.05-1.23)	0.09
NON VACCINATED	7(9.1%)	70(90.9%)	77		

Table.11

Odds Ratio: (2x70)/ (81x7) = 0.25. [CI (0.05-1.23)]

Assuming that all patients who were lost to follow up did not develop an acute exacerbation of COPD, there was no statistically significant association between vaccination status and development of an acute exacerbation of COPD. (p value = 0.09)

VACCINATION STATUS AND HOSPITALIZATION:

	HOSPITAL	NOT IN HOSPITAL	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	1(1.2%)	82(98.8%)	83	0.14 95%CI (0.02-1.23)	0.04
NON VACCINATED	6(7.8%)	71(92.2%)	77		

Table.12

Odds Ratio: (71x1)/ (82x6) = 0.14. [CI (0.02-1.23)]

Assuming that all patients who were lost to follow up were not hospitalized anywhere; there is a statistically significant association between vaccination status and hospitalization. (p value = 0.04)

VACCINATION STATUS AND MORTALITY:

	DEATH	NO DEATH	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	3(3.6%)	80(96.4%)	83	0.93 95%CI(0.18-4.73)	0.93
NON VACCINATED	3(3.9%)	74(96.1%)	77		

Table.13

Odds Ratio: (74x3)/ (80x3) = 0.93. [CI (0.18-4.73)]

Assuming that all patients lost to follow up are alive, there is no significant association between vaccination status and occurrence of death. (p value =0.93)

SUB GROUP ANALYSIS

A subgroup analysis was done with patients who developed respiratory symptoms and Chest X-ray positivity which was defined as a patch on chest X-ray.

14 patients who developed symptoms of fever and cough with yellow sputum had a patch on chest X-ray. Out of these patients with symptoms and a patch on chest X-ray, 13 were in the non vaccinated group and one was in the vaccinated group.

VACCINATION STATUS AND PATIENTS WITH SYMPTOMS AND XRAY POSITIVITY

	XRAY POSITIVE	XRAY NEGATIVE	TOTAL	ODDS RATIO	P-VALUE
VACCINATED	1(1.3%)	76(98.7%)	77	0.04 95%CI(0.006-0.364)	<0.001
NON VACCINATED	13(22.1%)	46(77.9%)	59		

Table.14

Odds Ratio: (46x1)/ (76x13) = 0.04. [CI (0.006-0.364)]

There was a statistically significant association between the vaccination status and development of respiratory symptoms with chest X-ray positivity. (p value < 0.001)

REASONS FOR NON VACCINATION : PATIENTS

Out of the 77 patients who did not want to be vaccinated, 55 (72%) [CI (61.3-81.5%)] were not able to afford the vaccine and cited the cost of the vaccine as the reason for not wanting the vaccination. 6 (8%) [CI (1.8-13.8%)] patients were not convinced of the beneficial effects of the vaccination, 10 (13%) [CI (5.5-20.5%)] patients did not want to be vaccinated as they had never experienced any of the outcomes which were described. The reason for non vaccination was not elicited in 5 (6%) [CI (0.99-11.9%)]of the

patients. 1 patient cited cost and not being symptomatic as the reason for not willing to be vaccinated.

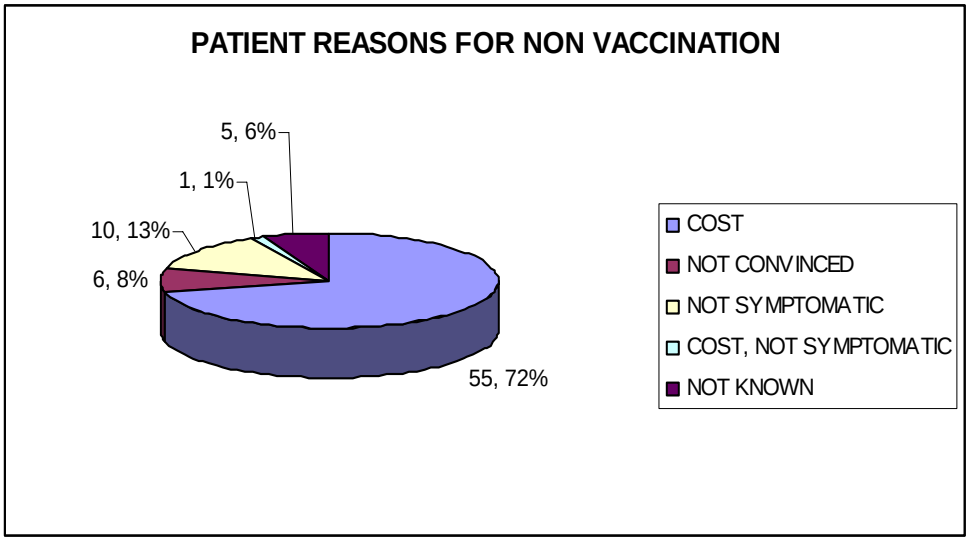


Fig.7

REASONS FOR NON VACCINATION- DOCTORS

The main reason cited by the physicians for not vaccinating patients was oversight. 8 of the 12 doctors who were interviewed said that oversight was one of the reasons for not prescribing pneumococcal vaccination. 6 doctors said that focusing on other medical problems caused them to not prescribe pneumococcal vaccination, whereas 5 doctors said that they did not prescribe the vaccine to all eligible patients due to the cost. None of the doctors cited the adverse effect related to the vaccine or a lack of evidence regarding the usefulness of the vaccine as a cause for non vaccination.

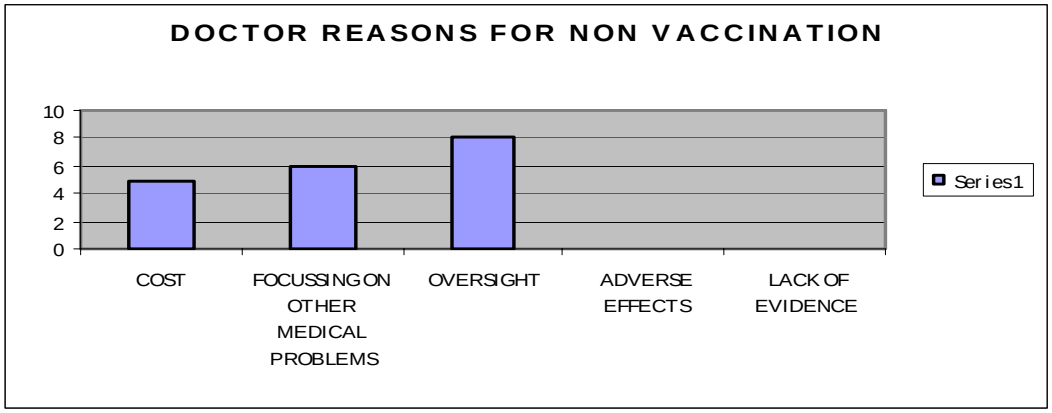


Fig.8

PRESCRIPTION PATTERN

Out of the 12 doctors who were interviewed, 9 cited old age and presence of lung diseases like chronic obstructive airways disease, asthma and interstitial lung disease as at least one of the reasons why they prescribed pneumococcal vaccine. 2 doctors said that patients with cardiac disease required vaccination, whereas 3 doctors said they prescribed pneumococcal vaccination for immuno compromised patients and 3 prescribed the vaccination to patients with Diabetes Mellitus. The other patient groups to whom the vaccine was being prescribed were patients who had had a stroke, those who had a previous history of community acquired pneumonia, patients who had undergone a splenectomy or patients who had a history of meningitis.

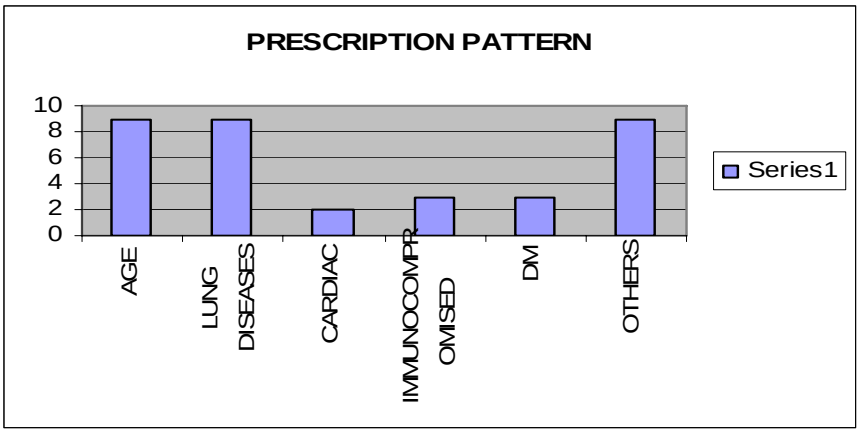


Fig.9

PRESCRIBING PRACTICES

6(50%) [CI (21.7-78.2%)] of the 12 doctors said that they occasionally prescribed the vaccine, whereas 4 (33%) [CI (6.7-60%)] said that they usually prescribed the vaccine. 1(8.3%) [CI (-7.3 – 24%)] physician always prescribed the vaccine whereas 1(8.3%) [CI (-7.3 – 24%) never prescribed the vaccine.

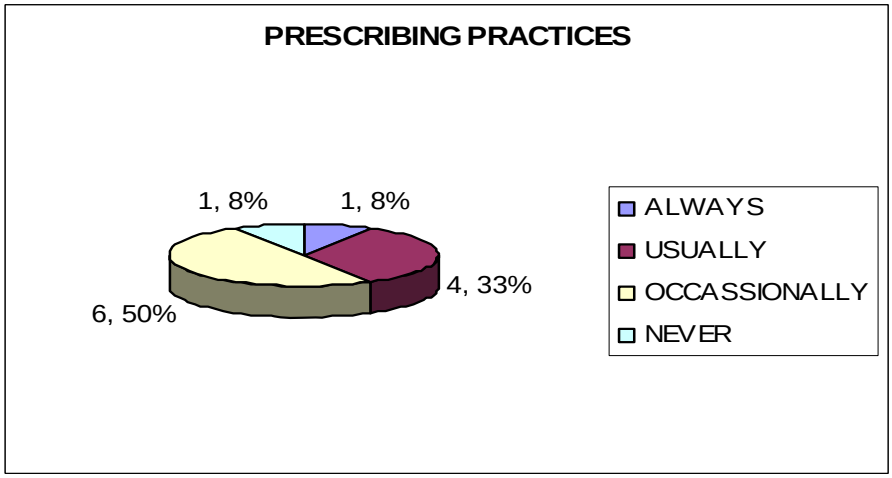


Fig.10

DISCUSSION

VACCINATION STATUS AND OUTCOMES

The protective efficacy of 23 valent pneumococcal vaccine (PV23) in preventing severe invasive pneumococcal disease is well established (44, 45, 48). However PV23 is not part of routine adult immunization in our country and very few eligible patients receive the same due to poor understanding on the role of adult immunization in our country and doubts about efficacy against serotypes prevalent in India. The present nested case control study reaffirms the role of PV23 in our setting for eligible patients. Even though Randomized control trials are needed to confirm the efficacy of an intervention, cohorts and nested case control designs are easier to perform with limited resources.

Among the 83 patients who were vaccinated, only 14 (17%) [CI (8.8-24.9%)] developed outcomes, while among the 77 patients who were vaccinated, 39 (50%) [CI (39.5-61.8%)] developed symptoms. Thus the overall protective efficacy of the vaccination against outcomes like development of respiratory infections was 89% [CI (75-95%)] according to this study. This was statistically significant with a p value <0.001. This is similar to the study done by the Centre for Disease Control and Prevention between May 1978 and April 1992 where they evaluated the efficacy of the vaccination among various risk groups and reported a 75% efficacy (95% CI, 57% to 85%) (51). This protective efficacy was statistically significant even in a sensitivity analysis, that is, when all the patients who were lost to follow up were assumed to have no outcomes during the study period (p value < 0.001). Thus it can be safely said that Pneumococcal vaccination has an important role in the health care of adult population today.

This study also showed a protective efficacy of 86% [CI (68-94%)] of the vaccine against development of respiratory infections as described by the symptomatology of fever and cough with yellow sputum where 9 (10.8%) [CI (4.1-17.5%)] of the vaccinated patients developed respiratory symptoms as compared to 29 (37.7%) [CI (26.8-48.5%)]of the non vaccinated group of patients. It also showed a protective benefit of the vaccine against development of pneumonia (respiratory symptoms with chest x-ray evidence). Only one patient among the vaccinated had a patch on chest x-ray along with lower respiratory symptoms as compared to 13 of the non vaccinated group of patients. Assuming that all the patients who were lost to follow up did not develop pneumonia, this result was still statistically significant (p value < 0.001). This is comparable to the EVAN-65 study which studied the protective benefit of pneumococcal vaccination among adults above 65 years and showed an overall reduction in the overall pneumonia rate HR, 0.79; 95% CI, 0.64–0.98) (48). The study also showed a protective benefit in reducing the number of acute exacerbations of COPD. Out of the 9 patients who developed a COPD exacerbation, 2 were in the vaccinated group and 7 were in non vaccinated group. However, when all the patients who were lost to follow up were assumed to be free of COPD exacerbations, this failed to achieve statistical significance (p value= 0.089). This was in contrast to earlier studies which failed to show a benefit among patients with COPD (50).

There was a protective benefit against hospitalizations associated with pneumonia and exacerbations of COPD according to this study. Of the 7 patients who were hospitalized for various outcomes, 6 belonged to the non vaccinated group. This was statistically significant with a p value of 0.04. However, the criteria for hospitalization were not

validated and the decision to hospitalize was not taken by a single examiner in all cases. This drawback has been considered as a limitation of this study. However, the reduction in risk for hospitalization among vaccinated individuals have been shown earlier in other big trials like the EVAN-65 trial (48).

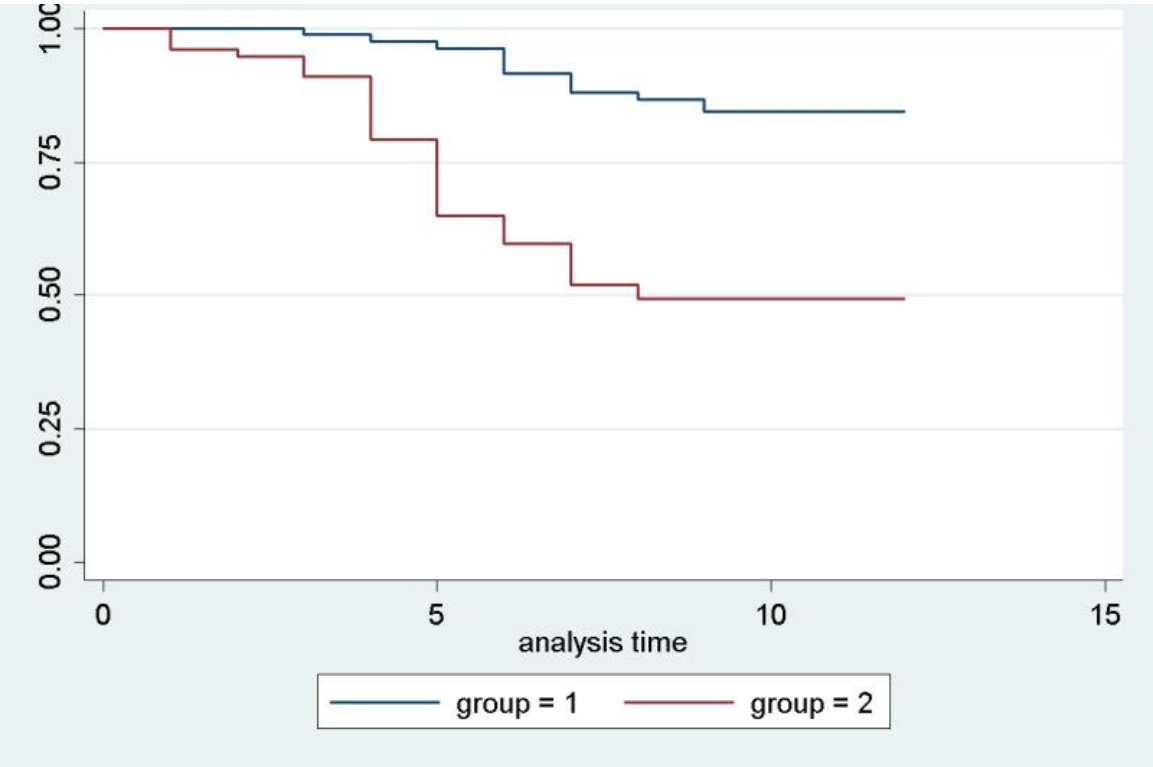
In this study, there was no protective benefit from death for people who received the pneumococcal vaccination. 3 people each from both the study arms died during the course of the study. 2 of these patients died of Type II respiratory failure during an acute exacerbation of COPD. Both of these patients were from the non vaccinated group. 3 patients died of myocardial infarction and in one patient, the cause of death had not been determined. This is in contrast to many of the older studies which have clearly demonstrated a definite reduction in the risk of death (48, 49). However, this could probably be attributed to the fact that the follow up period was much shorter in this study as compared to previous studies. A longer follow up period is required to demonstrate a reduction in the risk of death.

SURVIVAL ANALYSIS AND LOG RANK TEST

The Survival Analysis and the Log rank test which was used to evaluate the time to outcome of both the vaccinated and non vaccinated groups of people showed that outcomes occurred at a significantly earlier time in the non vaccinated group. About 50% of the non vaccinated patients had already had an outcome by the 8^{th} month of follow up. In the vaccinated group, 50% of the people had not yet had an outcome during the study period. This is due to the fact that the study period was very short. However, the difference in the time to outcome was statistically significant with a p value of <0.01.

TIME TO COMPOSITE OUTCOME

Kaplan Meier estimates



p value <0.01

group1=vaccinated

group2=non vaccinated

Fig.11

RATE OF VACCINATION

This study showed a rate of vaccination of 1.03% [CI (0.93-1.13%)] among the eligible patients who visit the Medical OPD. It is evident from this observation that only small proportion of eligible patients are getting vaccinated in our OPD setting even though this finding is limited by the fact that the seasonal variation and various other factors contributing to the patients' visits to the OPD have not been taken into account. It

confirms the fact that pneumococcal vaccination, and indeed all adult vaccinations are not being given to most of the patients who are eligible for vaccination. The rate of vaccination in our OPD is very low in comparison with other countries like the United States of America where reported rates range from 28.3% to 71.7% from different parts of the country (67).Therefore, it can be safely concluded that there is much room for improvement in this respect.

CAUSES OF NON VACCINATION

The majority of the people (72%) [CI (61.3-81.5%)] who were not willing to be vaccinated said that cost was the main factor deterring them from receiving the vaccination. The 23 valent Pneumococcal vaccine (Pneumo 23) costs Rs. 1050, which cannot be afforded by the majority of our population. Even though this may have a cost benefit in the long run, as the costs associated with a single episode of hospitalization will be much higher than this, more studies are needed in order to evaluate this. This also calls for better public health policies regarding adult vaccination. Cost effectiveness of the vaccine need to be widely understood even in our setting.

The main reasons cited by the doctors for not prescribing the vaccination were oversight and focusing on other medical problems. Most of the practitioners are not very familiar with the various adult vaccinations and their protective benefits. Adult vaccination forms an important part of preventive health measures in the community in the present age and all measures must be taken to keep the doctors' informed about these vaccines. It would be helpful to have immunization cards for adults as there are in children.

PRESCRIPTION PATTERN AND PRESCRIBING PRACTICES

The main groups of people to whom the vaccine was being prescribed were the elderly and patients with underlying lung diseases. Very few doctors considered Diabetes Mellitus as a risk factor requiring pneumococcal vaccination. In an earlier case control study done by Butler et al, it was shown that efficacy among persons with Diabetes Mellitus was 84%, with coronary vascular disease was 73% ,with congestive heart failure, 69%,with chronic pulmonary diseases, 65% and with anatomic asplenia, 77% (51). This shows that we need to vaccinate the people with Diabetes Mellitus and Coronary artery disease on a more regular basis.

50% [CI (21.7-78.2%)] of the doctors' said that they usually prescribed the vaccine; however, this is a misconception because the actual percentage of patients being vaccinated from the Medical OPD is only about 1 %.

LIMITATIONS

The study design was a nested case control study and not a randomized controlled trial. Subject allocation was not blinded. The subjects were recruited from OPD and later on assessed for development of outcomes by a single examiner, who was aware of the patient allocation. Therefore, the bias involved due to open assessment of outcomes cannot be excluded. An RCT gives the strongest empirical evidence of a treatment's efficacy. Randomization of participants to the test and control arms and concealment of their allocation ensures that allocation bias and confounding of unknown variables are minimized. Nested case control studies can however provide valid and precise estimates of associations and is a cost-effective alternative for full-cohort analysis.

Secondly, the rate of vaccination could have a wide error with regard to true measure of the number of subjects being vaccinated as the seasonal variation and other factors contributing to subjects' OPD visits have not been taken into account. The number of eligible subjects presenting to Medical OPD was taken only for a particular length of time and not for the entire one year.

Thirdly, there was a large number of subjects lost to follow up. About 15% of the study population has been lost to follow up. The number of subjects lost to follow up is not equally distributed among the cases and controls, most of the subjects who are lost to follow up belong to the non vaccinated group.

The study used clinical criteria alone as outcomes. This was not substantiated by laboratory criteria. Hence the presence of invasive pneumococcal disease in subjects with outcomes has not been proved.

There were no validated criteria for admission to the hospital. Hospitalization was not always decided by the investigating examiner. However, there may have been a bias in deciding which patient should have been hospitalized.

CONCLUSIONS

1) The percentage of eligible adult population presenting to Medical OPD who receive Pneumococcal vaccination is very low, currently1.03% [CI (0.93-1.13%)].There is need to increase awareness among practicing physicians to prescribe the correct dose to eligible groups of people.

2) The odds ratio for a patient with outcome (any one of the following- respiratory symptoms, exacerbation of COPD, hospitalization, death) being vaccinated is 0.11 [CI (0.05-0.25)]. This means that Pneumococcal vaccination confers an 89% protective effect against development of total outcomes ($p < 0.001$).

3) The odds ratio for a patient with symptoms of fever, cough and yellow sputum occurring during the study period being vaccinated is 0.14 [CI (0.06-0.32)] ie. Pneumococcal vaccination gives an 86% protective effect against symptoms of fever, cough and yellow sputum ($p < 0.001$).

4) The odds ratio for a patient with acute exacerbation of COPD occurring during the study period being vaccinated is 0.19 [CI (0.04-0.99)] showing a protective effect ($p=0.04$). However, when the patients who have been lost to follow up are also included in the analysis (sensitivity analysis), the protective effect becomes non significant. This tells us that exacerbations of COPD s influenced by multiple factors other than pneumococcal infection.

5) There were 7 hospitalized patients out of which one patient was vaccinated and 6 were not vaccinated. The odds ratio for patients who are hospitalized being vaccinated is 0.12 [CI (0.01-0.99)] which shows a statistically significant association between vaccination status and hospitalization (p= 0.04).

6) 3 vaccinated and 3 non vaccinated patients died during the study period. There was no protective association between Pneumococcal vaccination and death.

7) The main reason for subjects declining vaccination was the cost of the vaccine. 5 out of 77 patients (72%) [CI (61.3-81.5%)] considered cost as the leading reason for non vaccination. The other reasons were that at the time of recruitment, they were not symptomatic (10/77 patients =13%) [CI (5.5-20.5%)] or were not convinced (6/77 patients =8%)[CI(1.8-13.8%)] about the need for vaccination. In 5 out of 77 patients (6%) [CI (0.99-11.9%)], the reason for non vaccination could not be ascertained.

8) The main reasons for doctors' not prescribing the vaccine were due to oversight and focusing on other medical problems. None of the doctors thought that there was a lack of evidence regarding the protective efficacy of the vaccine.

9) The main patient groups to whom the vaccine was being prescribed were the elderly and patients who had underlying lung diseases.

10) 6 out of 12 doctors (50%) [CI (21.7-78.2%)] were of the opinion that they occasionally prescribed the vaccine whereas 4 out of 12 doctors (33%) [CI (6.7-60%)]

said they usually prescribed the vaccine. However, this is probably a misconception as only about 1 % of the eligible population is being vaccinated.

BIBLIOGRAPHY

1. Whitney CG, Schaffner W, Butler JC. Rethinking recommendations for use of pneumococcal vaccines in adults. Clin Infect Dis. 2001 Sep 1;33(5):662-75.

2. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med. 1995 Dec 14;333(24):1618-24.

3. Marrie TJ. Community-acquired pneumonia: epidemiology, etiology, treatment. Infect Dis Clin North Am. 1998 Sep;12(3):723-40.

4. High KP. Pneumonia in older adults. New categories add complexity to diagnosis and care. Postgrad Med. 2005 Oct;118(4):18-20, 5-8.

5. Fedson DS, Scott JA. The burden of pneumococcal disease among adults in developed and developing countries: what is and is not known. Vaccine. 1999 Jul 30;17 Suppl 1:S11-8.

6. Kalin M, Ortqvist A, Almela M, Aufwerber E, Dwyer R, Henriques B, et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. J Infect Dis. 2000 Sep;182(3):840-7.

7. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1997 Apr 4;46(RR-8):1-24.

8. Minino AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: final data for 2000. Natl Vital Stat Rep. 2002 Sep 16;50(15):1-119.

9. Obaro SK, Monteil MA, Henderson DC. The pneumococcal problem. BMJ. 1996 Jun 15;312(7045):1521-5.

10. Muder RR, Aghababian RV, Loeb MB, Solot JA, Higbee M. Nursing home-acquired pneumonia: an emergency department treatment algorithm. Curr Med Res Opin. 2004 Aug;20(8):1309-20.

11. Loeb M. Epidemiology of community- and nursing home-acquired pneumonia in older adults. Expert Rev Anti Infect Ther. 2005 Apr;3(2):263-70.

12. Jackson ML, Neuzil KM, Thompson WW, Shay DK, Yu O, Hanson CA, et al. The burden of community-acquired pneumonia in seniors: results of a population-based study. Clin Infect Dis. 2004 Dec 1;39(11):1642-50.

13. Inostroza J, Vinet AM, Retamal G, Lorca P, Ossa G, Facklam RR, et al. Influence of patient age on Streptococcus pneumoniae serotypes causing invasive disease. Clin Diagn Lab Immunol. 2001 May;8(3):556-9.

14. De Lencastre H, Kristinsson KG, Brito-Avo A, Sanches IS, Sa-Leao R, Saldanha J, et al. Carriage of respiratory tract pathogens and molecular epidemiology of Streptococcus pneumoniae colonization in healthy children attending day care centers in Lisbon, Portugal. Microb Drug Resist. 1999 Spring;5(1):19-29.

15. Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Engl J Med. 2000 Dec 28;343(26):1917-24.

16. Kupronis BA, Richards CL, Whitney CG. Invasive pneumococcal disease in older adults residing in long-term care facilities and in the community. J Am Geriatr Soc. 2003 Nov;51(11):1520-5.

17. Reinert RR, Haupts S, van der Linden M, Heeg C, Cil MY, Al-Lahham A, et al. Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001-2003. Clin Microbiol Infect. 2005 Dec;11(12):985-91.

18. Klugman KP. The successful clone: the vector of dissemination of resistance in Streptococcus pneumoniae. J Antimicrob Chemother. 2002 Dec;50 Suppl S2:1-5.

19. McGee L, McDougal L, Zhou J, Spratt BG, Tenover FC, George R, et al. Nomenclature of major antimicrobial-resistant clones of Streptococcus pneumoniae defined by the pneumococcal molecular epidemiology network. J Clin Microbiol. 2001 Jul;39(7):2565-71.

20. Reinert RR, van der Linden M, Seegmuller I, Al-Lahham A, Siedler A, Weissmann B, et al. Molecular epidemiology of penicillin-non-susceptible Streptococcus pneumoniae isolates from children with invasive pneumococcal disease in Germany. Clin Microbiol Infect. 2007 Apr;13(4):363-8.

21. Daneman N, McGeer A, Green K, Low DE. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. Clin Infect Dis. 2006 Aug 15;43(4):432-8.

22. Bauer T, Ewig S, Marcos MA, Schultze-Werninghaus G, Torres A. Streptococcus pneumoniae in community-acquired pneumonia. How important is drug resistance? Med Clin North Am. 2001 Nov;85(6):1367-79.

23. Balmer P, Borrow R, Findlow J, Warrington R, Frankland S, Waight P, et al. Age-stratified prevalences of pneumococcal-serotype-specific immunoglobulin G in England and their relationship to the serotype-specific incidence of invasive

pneumococcal disease prior to the introduction of the pneumococcal 7-valent conjugate vaccine. Clin Vaccine Immunol. 2007 Nov;14(11):1442-50.

24. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis. 2005 Feb;5(2):83-93.

25. Abdullahi O, Nyiro J, Lewa P, Slack M, Scott JA. The descriptive epidemiology of Streptococcus pneumoniae and Haemophilus influenzae nasopharyngeal carriage in children and adults in Kilifi district, Kenya. Pediatr Infect Dis J. 2008 Jan;27(1):59-64.

26. Prospective multicentre hospital surveillance of Streptococcus pneumoniae disease in India. Invasive Bacterial Infection Surveillance (IBIS) Group, International Clinical Epidemiology Network (INCLEN). Lancet. 1999 Apr 10;353(9160):1216-21.

27. Scott JA, Hall AJ, Dagan R, Dixon JM, Eykyn SJ, Fenoll A, et al. Serogroup-specific epidemiology of Streptococcus pneumoniae: associations with age, sex, and geography in 7,000 episodes of invasive disease. Clin Infect Dis. 1996 Jun;22(6):973-81.

28. Butler JC, Breiman RF, Lipman HB, Hofmann J, Facklam RR. Serotype distribution of Streptococcus pneumoniae infections among preschool children in the United States, 1978-1994: implications for development of a conjugate vaccine. J Infect Dis. 1995 Apr;171(4):885-9.

29. Dr. Kurien Thomas. IBIS Phase II Study. Personal communication.

30. Saha SK, Rikitomi N, Biswas D, Watanabe K, Ruhulamin M, Ahmed K, et al. Serotypes of Streptococcus pneumoniae causing invasive childhood infections in Bangladesh, 1992 to 1995. J Clin Microbiol. 1997 Mar;35(3):785-7.

31. Abarca VK, Vergara FR, Tassara PE, Ibanez WI, Garcia BC, Potin SM. [Invasive pneumococcal disease and consolidated pneumonia in infants: one year of surveillance in three Chilean health care centers]. Rev Chilena Infectol. 2008 Apr;25(2):97-103.

32. National Centre for Streptococcus. Annual Report for April 1, <http://www2.provlab.ab.ca/bugs/vlab/ncs/ar2000_2.pdf> tM. [cited]; Available from.

33. Tang K GA, McGeer K, et al. . Antibiotic resistance trends in Canadian strains of Streptococcus pneumoniae: Results from 9 consecutive years of surveillance. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy Sep 29, 2002 San Diego, California,. Sep 29, 2002

34. Pletz MW, Maus U, Krug N, Welte T, Lode H. Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. Int J Antimicrob Agents. 2008 Mar 29.

35. Ada G. Vaccines and vaccination. N Engl J Med. 2001 Oct 4;345(14):1042-53.

36. Stephen TL, Fabri M, Groneck L, Rohn TA, Hafke H, Robinson N, et al. Transport of Streptococcus pneumoniae capsular polysaccharide in MHC Class II tubules. PLoS Pathog. 2007 Mar;3(3):e32.

37. Rose MA, Schubert R, Strnad N, Zielen S. Priming of immunological memory by pneumococcal conjugate vaccine in children unresponsive to 23-valent polysaccharide pneumococcal vaccine. Clin Diagn Lab Immunol. 2005 Oct;12(10):1216-22.

38. Wright AE PMW, Colebrook L, Dodgson RW. Observations on prophylactic inoculation against pneumococcus infections, and on the results which have been achieved by it. Lancet 1914;1:1-10, 87-95

39. . AR. Life with the pneumococcus: notes from the bedside, laboratory, and library. Philadelphia: University of Pennsylvania Press,; 1985.

40. Stein KE. Thymus-independent and thymus-dependent responses to polysaccharide antigens. J Infect Dis. 1992 Jun;165 Suppl 1:S49-52.

41. Musher DM, Luchi MJ, Watson DA, Hamilton R, Baughn RE. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and the effect of adsorption of serum with non-type-specific cell wall polysaccharide. J Infect Dis. 1990 Apr;161(4):728-35.

42. Ammann AJ AK, Wara DW, Lubin D, Smith WB, Mentzer WC. Poly valent pneumococcal-polysaccharide immunization of patients with sickle cell anemia and patients with splenectomy. N Engl J Med. 1977;297:897-900.

43. E. Herva JL, M. Timonen, M. Sibakov, P. Karma and P.H. Makela. The effect of polyvalent pneumococcal polysaccharide vaccine on nasopharyngeal and nasal carriage of *Streptococcus pneumoniae*. Scand J Infect Dis 1980;12::97-100.

44. Mykietiuk A, Carratala J, Dominguez A, Manzur A, Fernandez-Sabe N, Dorca J, et al. Effect of prior pneumococcal vaccination on clinical outcome of hospitalized adults with community-acquired pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis. 2006 Jul;25(7):457-62.

45. M.J. Fine DES, B.H. Hanusa, J.R. Lave and W.N. Kapoor. Validation of a pneumonia prognostic index using the MedisGroups Comparative Hospital Database. Am J Med 94(1993):153-9.

46. Hutchison BG, Oxman AD, Shannon HS, Lloyd S, Altmayer CA, Thomas K. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. Can Fam Physician. 1999 Oct;45:2381-93.

47. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005 Mar 26-Apr 1;365(9465):1139-46.

48. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. Lancet. 2001 Mar 31;357(9261):1008-11.

49. Fine M.J. SMA, Carson C.A., et al. . Prognosis and outcomes of patients with community-adquired pneumonia. . JAMA. 1996;275:134-41.

50. ;. Influenza and pneumococcal vaccination levels among adults aged > 65 years. United States. . In: Prevention CfDCa, editor.; 1998. p. 797-802.

51. Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodriguez T, et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis. 2006 Oct 1;43(7):860-8.

52. Vila-Corcoles A, Ochoa-Gondar O, Llor C, Hospital I, Rodriguez T, Gomez A. Protective effect of pneumococcal vaccine against death by pneumonia in elderly subjects. Eur Respir J. 2005 Dec;26(6):1086-91.

53. Loeb M, Stevenson KB. Pneumococcal immunization in older adults: implications for the long-term-care setting. Infect Control Hosp Epidemiol. 2004 Nov;25(11):985-94.

54. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA. 1993 Oct 20;270(15):1826-31.

55. Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era. JAMA. 2001 Apr 4;285(13):1729-35.

56. Watera C, Nakiyingi J, Miiro G, Muwonge R, Whitworth JA, Gilks CF, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. AIDS. 2004 May 21;18(8):1210-3.

57. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med. 2000 Feb 1;132(3):182-90.

58. Lee TA, Weaver FM, Weiss KB. Impact of pneumococcal vaccination on pneumonia rates in patients with COPD and asthma. J Gen Intern Med. 2007 Jan;22(1):62-7.

59. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. Clin Infect Dis. 1998 Mar;26(3):590-5.

60. Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med. 2000 Mar 9;342(10):681-9.

61. Nuorti JP, Butler JC, Crutcher JM, Guevara R, Welch D, Holder P, et al. An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. N Engl J Med. 1998 Jun 25;338(26):1861-8.

62. Fiore AE, Iverson C, Messmer T, Erdman D, Lett SM, Talkington DF, et al. Outbreak of pneumonia in a long-term care facility: antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia. J Am Geriatr Soc. 1998 Sep;46(9):1112-7.

63. Quick RE, Hoge CW, Hamilton DJ, Whitney CJ, Borges M, Kobayashi JM. Underutilization of pneumococcal vaccine in nursing home in Washington State: report of a serotype-specific outbreak and a survey. Am J Med. 1993 Feb;94(2):149-52.

64. Outbreaks of pneumococcal pneumonia among unvaccinated residents of chronic-care facilities--Massachusetts, October 1995, Oklahoma, February, 1996, and Maryland, May-June 1996. MMWR Morb Mortal Wkly Rep. 1997 Jan 24;46(3):60-2.

65. Active Bacterial Core Surveillance (ABCs) Report. Emerging Infections Program Network: *Streptococcus pneumoniae*. In: Prevention CfDCa, editor.; 1999.

66. Hofmann J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliott JA, et al. The prevalence of drug-resistant Streptococcus pneumoniae in Atlanta. N Engl J Med. 1995 Aug 24;333(8):481-6.

67. Zangwill KM, Vadheim CM, Vannier AM, Hemenway LS, Greenberg DP, Ward JI. Epidemiology of invasive pneumococcal disease in southern California: implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. J Infect Dis. 1996 Oct;174(4):752-9.

68. Davidson M, Parkinson AJ, Bulkow LR, Fitzgerald MA, Peters HV, Parks DJ. The epidemiology of invasive pneumococcal disease in Alaska, 1986-1990--ethnic differences and opportunities for prevention. J Infect Dis. 1994 Aug;170(2):368-76.

69. Cortese MM, Wolff M, Almeido-Hill J, Reid R, Ketcham J, Santosham M. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med. 1992 Nov;152(11):2277-82.

70. Harrison LH, Dwyer DM, Billmann L, Kolczak MS, Schuchat A. Invasive pneumococcal infection in Baltimore, Md: implications for immunization policy. Arch Intern Med. 2000 Jan 10;160(1):89-94.

71. Influenza and pneumococcal vaccination coverage among persons aged > or = 65 years--United States, 2004-2005. MMWR Morb Mortal Wkly Rep. 2006 Oct 6;55(39):1065-8.

72. Nowalk MP, Zimmerman RK, Tabbarah M, Raymund M, Jewell IK. Determinants of adult vaccination at inner-city health centers: a descriptive study. BMC Fam Pract. 2006;7:2.

73. Andrews RM, Skull SA, Byrnes GB, Campbell DA, Turner JL, McIntyre PB, et al. Influenza and pneumococcal vaccine coverage among a random sample of hospitalised persons aged 65 years or more, Victoria. Commun Dis Intell. 2005;29(3):283-8.

74. Bansal S, Kashyap S, Pal LS, Goel A. Clinical and bacteriological profile of community acquired pneumonia in Shimla, Himachal Pradesh. Indian J Chest Dis Allied Sci. 2004 Jan-Mar;46(1):17-22.

75. Jamal F. Epidemiological data on pneumococcal infections in Asian countries. Vaccine. 1999 Jul 30;17 Suppl 1:S75-8.

76. Thacker N. Integrated management of neonatal and childhood illnesses: a new hope for child survival. Indian Pediatr. 2007 Mar;44(3):169-71.

PATIENT PROFORMA

Name:

Sex:

Marital status: M/U

Hospital Number:

Age:

Address:

Telephone number:

Criteria for inclusion into the study: Yes/ No

1. Age above 60
2. Underlying pulmonary disease
3. Underlying cardiac disease
4. Immunocompromised states
5. Diabetes Mellitus
6. Chronic renal failure
7. Liver disease
8. Haematological conditions

Vaccination status: Yes/ No

Date of vaccination:

Reason for unwillingness:
(not vaccinated)

1	Cost
2	Not convinced
3	Not symptomatic
4	Not known
5	Others

OUTCOME DETAILS

OUTCOME	BLOOD CULTURE	CSF GRAM STAIN AND CULTURE	SPUTUM CULTURE	CHEST XRAY	HOSPITALISATION
COPD EXACERBATION					
PNEUMONIA					
MENINGITIS					

PATIENT FOLLOW UP

SUBJECT	Jul 07	Aug 07	Sep 07	Oct 07	Nov 07	Dec 07
OUTCOME						

SUBJECT	Jan 08	Feb 08	Mar 08	Apr 08	May 08	Jun 08
OUTCOME						

SUBJECT	Jul 08	Aug 08
OUTCOME		

Date of vaccination:

Number of outcomes:

INFORMED CONSENT FORM

TITLE OF THE STUDY: The use of pneumococcal vaccine in a tertiary care centre in India

INSTITUTION: Department of Medicine II, Christian Medical College and Hospital.

HOSPITAL NO.:

NATURE AND PURPOSE OF THE STUDY: You are being asked to participate in a study which involves receiving pneumococcal vaccine and being followed up for a period of 6 months to one year to assess the efficacy of the vaccine.

Benefits of being vaccinated: Pneumococcal disease is a serious disease which results in much sickness and death. It can cause very serious infections in the lung (pneumonia), brain (meningitis) or blood (bacteremia).There is documented resistance to drugs like Penicillin, hence prevention through vaccination becomes important.

Adverse effects of the vaccination: It is mostly a safe vaccine. However it can cause minor side effects like

- redness and pain at the site of injection.(50%)
- fever, muscle aches or more severe local reactions.(<1%)
- very rarely, severe allergic reactions.

EXPECTED DURATION OF INVOLVEMENT: Duration of assessment will be for about 6 months to one year.

POSSIBLE BENEFITS OF THE STUDY: The outcome of the study will help us to know the protective efficacy of the vaccine and the various reasons of non vaccination in our adult population. You will not be charged for the vaccine or the urine BINAX test.

CONFIDENTIALITY: Your records and all details obtained in this study will remain strictly confidential at all times, but will need to be available to the doctor conducting the study. Your identity will not otherwise be revealed. Your personal data collected will be processed only for research purposes in connection with this study. You will not be referred to by name or identified in any report or publication.

RIGHT TO WITHDRAW FROM THE STUDY: You are free to leave the study at any time. Your decision not to participate in this study will not affect your present or future medical care.

CONSENT: I have read/ had read to me above information before signing this consent form.

SIGNATURE OF THE SUBJECT:

SIGNATURE OF THE PERSON OBTAINING CONSENT:

DATE:

QUESTIONNAIRE FOR THE DOCTORS

1.AGE

2.SEX

M F

3.NUMBER OF YEARS OF CLINICAL EXPERIENCE POST MD

4.IN WHICH PATIENTS DO YOU GENERALLY PRESCRIBE PNEUMOCOCCAL VACCINE? PLEASE STATE

5.ARE YOU PRESCRIBING PNEUMOCOCCAL VACCINE TO ALL PATIENTS WHO YOU THINK REQUIRE TO BE VACCINATED?

1- always
2- usually
3- occasionally
4- never

7.IF THE ABOVE ANSWER IS 3 OR 4 ,STATE YOUR REASONS.

1- Cost
2- Focusing on other medical problems
3- Oversight
4- Lack of evidence regarding efficacy
5- Adverse effects of the vaccine
6- Others (Please state)

DATA FOR THESIS

1. To determine the rate of pneumococcal vaccination among adult patients fulfilling the general indications for vaccination in Medicine OPD.
   No. of eligible patients in one week: 829
   No. of vaccinations in 8 months: 296

2. Data for EXCEL sheet
   Male 1
   Female 2

   Vaccinated 1
   Non vaccinated 2

   Outcome
   1. COPD Exacerbation
   2.
   3. Meningitis
   4. Bactremia
   5. Pneumonia
   6. No complaints
   7. Death
   8. Hospitalisation

   Labs
   1.Blood c/s
   2.CSF
   3.Sputum c/s
   4.CXR
   5.
   6. Not applicable/ nil

   Reason for non vaccination
   1.cost
   2.not convinced
   3.Not symptomatic
   4.not known
   5. not applicable

Cause of death
1.Pneumonia
2.Meningitis
3. Acute exacerbation
4.others
5. not known

Lost to follow up:23

Prescription
1. Age
2. Underlying lung disease
3. Underlying cardiac disease
4. Immunocompromised
5. Diabetes Mellitus
6. Chronic renalfailure
7. Liver disease
8. Haematological conditions
9. Others

Pattern
1.always
2.usually
3. occasionally
4.never

NAME	HOSP.NO	AGE	SEX	RISK FACTORS
VIJAYA	837224	48	2	5
SAMPATH	025401B	43	1	5
VISALAKSHI	945129C	66	2	1,5
SUBRAMANIAM	577102B	60	1	5
ARUMUGAM	014000D	78	1	1,5
JEYARAMAN	025401B	65	1	1,2,5
VENNILA	286914C	53	2	5
BERNADETTE	840378	64	2	1
JEYAGOPI	482993C	49	1	5
VASANTHA	125005D	67	2	1,5
SUNDARESAN	540718B	72	1	1,2,3,5
VACCHALA	153177D	61	2	1,5
ACHUTHAN	796825C	65	1	1,5
THAYYAN	176669C	75	1	1,2,5
THIRUPURAMMA	469978A	68	2	1,2,5
SELVARAJ	23168	68	1	1,3,5
NAVANEETHAM	104448D	70	2	1,5
PONNACHI	130078B	79	2	1,2
ARUGADAN	156150C	62	1	1,5
SRI RAMULU	128978B	72	1	1,2,5
ARUMUGAM	14000	78	1	1
THARABAI	014674D	56	2	5
PARIMALA	385455	61	2	1,5
SULAIMAN	183183C	52	1	5
CHANDRASEKHAR	236770	70	1	1,5
RAJAMMA	395691	54	2	3,5
PONNAIYAN	223274A	61	1	1,3,5
NISAR AHMED	334967C	50	1	3,5
RAJENDRAN	734410C	54	1	5
BASHEER AHMED	993015B	57	1	2,5
CHANDRA .P	162606D	54	2	5
ISRAEL	814213A	77	1	1,2,5
SAMBANDAN	448737C	66	1	1,5
PRAKASAM	271337	64	1	1,2
RAJENDRAN	027890D	49	1	5
SYED NIZAR	608308B	65	1	1,5
CHAKARAI	674733C	48	1	2,5
KUMARAVEL	950439B	47	1	2,3,5
EKAMBARAM	473217C	74	1	1,5
LAKSHMI	137631D	50	2	5
PACHAIYAMMAL	907093C	56	2	3,5
ANANDAN	185416D	49	1	5
NIRMALA	159093C	70	2	1,3,5
UBAYADULLAH	978104C	53	1	5
NATARAJAN	778053C	47	1	5
ARJUNAN	142171D	73	1	1,2,5
LILLY MUNISAMY	038174D	67	2	1,3,5
FAKKURUDIAN	436762C	66	1	1,3,5
MUTHUMANICKAM	137964D	71	1	1,3,5
MOORTHY	026920C	55	1	5

ABDUL RASHID	164653D	79	2	1,2
PUGHAZHENDI	555084A	49	1	5
SEETHARAMAN	230643	72	1	1,2
JAYALAXMI	767856C	54	2	5
SHAKUNTALA	951834B	57	2	3,5
EKAMBARAM	281711C	67	1	1,2,5
MANI K	169009D	62	1	1,2,5
PARVATHY	658927C	55	2	5
RAJA D	354426C	49	1	3,5
ARJUNAN V	143120D	65	1	1,2
GOVINDAN	143220D	62	1	1,2
SUSHEELA	669944C	76	2	1,2
RAJAGOPAL	975657C	65	1	1,2
GNANA WILSON	647508C	62	1	1,2,5
PADMANABHAN	675256C	82	1	1
SHANTA	32`549B	70	2	1
CHANDRA .M	162600D	54	2	5
ANANDAN	143114D	40	2	2,5
MURALIDHARAN	196144D	36	1	5
DURAIRAJ	194029D	44	1	5
ARUNACHALAM	259653	71	1	1
SARADHA	545057	77	2	1,2
MERCY	676760A	82	2	1,2,5
RAMAJEYAM	160703D	60	1	2
SUBRAMA NI	775293C	38	1	2
SARADHA	545068B	77	2	1,2,3
ESWARAN	266508C	51	1	2
BHAGAVAN DASS	567128B	63	1	1,2,5
AMMENI G	184018D	64	2	1,3
VIJAYA	799272C	48	2	5
KANNIAPPAN	965948C	58	1	2
JEYAKUMAR	811858A	56	1	5
BALA	923585	62	2	1,5
RANGANATHAN	445936C	61	1	1,5
DURAI	166215D	75	1	1,2
VENKATCHALPATHI	466673	74	1	1,2,3
SURESH	048164D	46	1	5
PATTAMMAL	577305A	68	2	1
POWN DEVARAJ	152145D	49	2	5
VINCENT	186166	64	1	1,2
MOSES	223517	66	1	1,5
PAWNAMMAL	061526D	50	2	5
GOWRIAMMAL	199735B	70	2	1,5
MURUGESAN	516817B	64	1	1,2
KRISHNAVENI	497459A	52	2	5
VEERABADRAN	312693B	74	1	5
PARVATHI	404601C	44	2	5
KASTHURI	563581A	57	2	5
KRISHNAMOORTHY	626051C	53	2	2
NAVANEETHAM	156002C	52	2	5
PONNUSAMY	252152	62	1	1,5

DEVARAJ	208104D	67	1	1,2
VENKATESAN	221465D	63	1	1,2
SUBRAMANI	162948C	80	1	1,5
LAKSHMI	927824B	67	2	1
SESHALAM	303288B	69	1	1,5,6
RAJAMMA	168069D	70	2	1
RAMBAI AMMAL	341386B	69	2	1,5
RAHIMUNISA	683677B	59	2	5
RADHA.P	521703C	68	2	1,5
BANU	130333D	50	2	2,5
VELAUDHAM	722875B	52	1	5
GAJENDRAN	116738C	45	1	6
KANNAMMAL	971985C	70	2	1
KANNAGOUNDER	504278C	63	1	1,6
GANESAN	331892	66	1	1,5
RAJAMANI	672261C	44	1	3,5
KUPPAMMA	976712C	45	2	5
PANNEER.V	354600C	59	1	5
YESTHER	107564	52	2	5
EDWAD JONES	41555	81	1	1,2,5
KUPPAMMA	405531C	52	2	2,5
NICKELSEN	781095C	52	1	5
VEERAMANI	893209C	40	1	5
BOMMI	651222A	51	2	5
GOVINDASAMY	608645A	53	1	2
BOOPALAN	399530	73	1	2
GRACE PUNITHA	493374C	58	2	5
NAGARAJAPILLAI	701245A	74	1	1,5
ATTODIL	604152A	65	2	1,2,5
DURAIKRISHNAN	448394B	72	1	1,5
DHANAM	506921	59	2	5
PATTAMMAL	965974C	75	2	1
KANNIAMMAL	100375D	60	2	5
MAHMATH BASHA	489916C	47	1	3,5,6
JEBAKANI	374234A	72	2	1,2
PONNUSAMY	647124C	67	1	1,2
MUNIAMMAL	211913D	65	2	1
SIVABHUSHANAM	125340	58	2	2,5
SUSHEELA	381655B	77	2	1,3
ANWAR BASHA	148845D	48	1	2,5
MANGALAXMI	416256C	69	2	1,5
PALANIVEL	190072D	65	1	1
DEVANESAN	974929C	63	1	1,2,5
NATARAJAN	930576C	76	1	1,2,5
BABU	943459B	72	1	1,2
LAKSMANAN	918487C	79	1	1,2
VISHWANATHAN	289426C	62	1	1,5
LAKSHMI	564992C	55	2	5
YESUPATHAM	597344C	71	1	1,2
MOHAN N	466870C	58	1	5
SAROJA	881319C	67	2	1

KANNAYAN	305295B	67	1	1,5	
SUBRAMANIAM	598650B	64	1	1,5	
VELU	208812D	70	1		1
THAVAMANI	903218C	60	2	2,5	
JAYACHANDRAN	797222B	50	1		2
GEETHESWARI	753666B	55	2		2
ARPUTHA MMAL	703827A	88	2	1,5	
JANARDHANAM	296975B	68	1	1,2,5	

VACCINATION STAT	DATE OF VACCINAT	OUTCOME	DATE C	PNEUMONIA	COPD
1	12.07	6		1	1
1	12.07	5	6.08	2	1
1	12.07	5	6.08	2	1
2	7.07	6		1	1
1	12.07	6		1	1
1	10.07	1	4.08	1	2
2	12.07	6		1	1
1	12.07	5	6.08	2	1
2	11.07	6		1	1
2	10.07	5	4.08	2	1
1	12.07	6		1	1
1	12.07	6		1	1
1	11.07	6		1	1
1	11.07	6		1	1
1	7.07	6		1	1
1	11.07	6		1	1
1	11.07	7	6.08	1	1
1	11.07	6		1	1
1	11.07	6		1	1
1	11.07	6		1	1
2	11.07	5,5	12.07,0	2	1
1	11.07	6		1	1
2	11.07	6		1	1
1	12.07	6		1	1
1	9.07	6		1	1
1	12.07	6		1	1
1	12.07	6		1	1
1	9.07	6		1	1
2	11.07	5,8	4.08	2	1
2	12.07	1	7.08	1	2
2	11.07	8	1.08	2	1
2	9.07	6		1	1
1	7.07	6		1	1
1	7.07	1	4.07	1	2
1	11.07	6		1	1
1	11.07	6		1	1
2	11.07	6		1	1
2	11.07	1	6.08	1	2
2	7.07	6		1	1
2	9.07	6		1	1
1	9.07	6		1	1
1	9.07	6		1	1
1	11.07	6		1	1
1	11.07	6		1	1
2	11.07	6		1	1
2	7.07	5,7,8	11.07	2	1
1	11.07	6		1	1
2	11.07	7	12.07	1	1
2	11.07	6		1	1
1	11.07	6		1	1

2	10.07	7,8		1.08	1	1
1	12.07		6		1	1
1	8.07		6		1	1
2	9.07		6		1	1
1	9.07		6		1	1
2	11.07		1	4.08	1	2
2	9.07		5	1.08	2	1
2	9.07		5	3.08	2	1
2	7.07		5	12.07	2	1
2	7.07		5	11.07	2	1
2	7.07	1,8		12.07	1	2
1	12.07		6		1	1
2	9.07		5	1.08	2	1
2	7.07		5	12.07	2	1
2	9.07		5	12.07	2	1
2	10.07		5	11.07	2	1
2	10.07		5	1.08	2	1
2	7.07	1,8		11.07	1	2
2	7.07		5	3.08	2	1
2	7.07		5	2.08	2	1
2	8.07		5	1.08	2	1
2	12.07		1	7.08	1	2
2	10.07		1	1.08	1	2
2	12.07		5	3.08	2	1
2	7.07		5	2.08	2	1
1	10.07		6		1	1
2	7.07		5	2.08	2	1
2	8.07		5	12.07	2	1
2	1.08		5	5.08	2	1
2	10.07		5	3.08	2	1
1	8.07	5,8		4.08	2	1
1	11.07		6		1	1
1	1.08		7	5.08	1	1
1	10.07		6		1	1
2	1.08		6		1	1
2	10.07		5	11.07	2	1
1	7.07		6		1	1
2	7.07		5	1.08	2	1
2	7.07	5,8		12.07	2	1
1	9.07		5	3.08	2	1
1	7.07		5	2.08	2	1
1	9.07		6		1	1
1	9.07		6		1	1
1	1.08		6		1	1
2	9.07					
2	12.07		5	5.08	2	1
1	8.07		6		1	1
2	12.07					
2	10.07					
2	12.07					
1	11.07		6		1	1

1	12.07	6		1	1
1	12.07	6		1	1
1	12.07	6		1	1
2	8.07				
2	11.07				
1	1.08				
2	7.07				
2	9.07				
2	11.07				
2	10.07				
1	8.07				
2	9.07				
2	10.07	6		1	1
2	9.07	6		1	1
1	10.07	6		1	1
2	8.07	5	5.08	2	1
2	9.07				
2	10.07				
2	7.07	6		1	1
2	7.07	6		1	1
2	10.07				
2	8.07				
1	10.07	6		1	1
2	11.07				
2	7.07				
1	7.07	6		1	1
2	8.07	6		1	1
1	9.07	6		1	1
1	12.07				
1	7.07				
2	7.07	6		1	1
2	9.07	6		1	1
2	9.07	6		1	1
2	8.07	6		1	1
1	9.07	6		1	1
1	7.07				
2	12.07	5	5.08	2	1
1	8.07	6		1	1
1	12.07				
1	1.08	6		1	1
1	12.07	6		1	1
2	12.07				
1	7.07	6		1	1
1	7.07	6		1	1
1	7.07	5	3.08	2	1
1	10.07	6		1	1
1	8.07	6		1	1
1	11.07	6		1	1
1	8.07	6		1	1
1	12.07	6		1	1
1	12.07	7	6.08	1	1

1	12.07	6		1	1
1	12.07	6		1	1
1	12.07	6		1	1
1	12.07	5	5.08	2	1
1	11.07	6		1	1
1	9.07	6		1	1
1	7.07	6		1	1
1	8.07	5	11.07	2	1

HOSPITALISATION	DEATH	COMPLAIN	LABS	OUTCOME	REASON FOR NON VACCINATION
1	1	1	6		5
1	1	2	6	1	5
1	1	2	3	2	5
1	1	1	6		3
1	1	1	6		5
1	1	2	6	1	5
1	1	1	6		1
1	1	2	3	2	5
1	1	1	6		2
1	1	2	6	1	3
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	2	2	6	1	5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	2	6	1	1
1	1	1	6		5
1	1	1	6		1
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		1
2	1	2	6		1
1	1	2	6	1	1
1	1	2	4	2	1
1	1	1	6		1
1	1	1	6		5
1	1	2	6	1	5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		1
1	1	2	6	1	2
1	1	1	6		3
1	1	1	6		1
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		1
2	2	2	3,4	2	1
1	1	1	6		5
1	2	2	6	1	5
1	1	1	6		3
1	1	1	6		5

2	2	2	6	1	1
1	1	1	6		5
1	1	1	6		5
1	1	1	6		2
1	1	1	6		5
1	1	2	6	1	1
1	1	2	3	2	1
1	1	2	4	2	1
1	1	2	4	2	2
1	1	2	3,4	2	1
2	1	2	6	1	1
1	1	1	6		5
1	1	2	3	2	1
1	1	2	4	2	2
1	1	2	3	2	3
1	1	2	4	2	1
1	1	2	4	2	1
2	1	2	6	1	1
1	1	2	4	2	3
1	1	2	4	2	1
1	1	2	3	2	2
1	1	2	6	1	1
1	1	2	6	1	1
1	1	2	4	2	1
1	1	2	6	1	1
1	1	1	6		5
1	1	2	6	1	1
1	1	2	3	2	1
1	1	2	6	1	1
1	1	2	4	2	1
2	1	2	1,3,4	2	5
1	1	1	6		5
1	2	2	6	1	5
1	1	1	6		5
1	1	2	6	1	1
1	1	2	6	1	1
1	1	1	6		5
1	1	2	6	1	3
2	1	2	4	2	3
1	1	2	3	2	5
1	1	2	3	2	5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	2		1	1
1	1	1	6		5
					1
					1
1	1	1	6		5

1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
					5
					1
					1
					1
					1
					5
					1
1	1	1	6	1,3	
1	1	1	6		1
1	1	1	6		5
1	1	2		1	1
					1
					1
1	1	1	6		1
1	1	1	6		1
					1
					1
1	1	1	6		5
					3
					1
1	1	1	6		5
1	1	1	6		1
1	1	1	6		5
					5
					5
1	1	1	6		1
1	1	1	6		3
1	1	1	6		1
1	1	1	6		1
1	1	1	6		5
					5
1	1	2		1	1
1	1	1	6		5
					5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	2	6	1	5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	1	6		5

1	1	1	6		5
1	1	1	6		5
1	1	1	6		5
1	1	2		1	5
1	1	1	6		5
1	1	1	6		5
1	2	2		1	5
1	1	2		1	5

CAUSE OF DEATH	ORGANISM
	Ps. Aeruginosa
	H. influenza
5	
3	Yeast, GPC
4	

3

Ps. Aeruginosa

Klebsiella

Klebsiella

Klebsiella

GPC in chainsand pairs
Strep. Pneumoniae

Klebsiella

Strep. Pneumoniae

4

Klebsiella
H. influenza

SR.NO	AGE	SEX	PRESCRI	PATTERN	REASONS	EXEPERIENCE
1	42	1	2,5	2	1,3	13
2	38	1	2,5,1,4	1	1,2,3	13
3	29	1		3	1,2	5
4	49	1	1,2,3,4,9	2	3	19
5	56	1	1	3	3	27
6	31	2	1,2,4	3	1,3	8
7	42	2	1	4	2	
8	35	2	1,2	2	2,3	11
9	44	1	1,2,3,9	2	2,3	17
10	30	1	2	3	3	10
11	34	2	1,2,5,9	3	2	11
12	37	2	1,2,9	3	1	12

NAME	HOSP.NO	VACCINATION STATUS	DATE OF ENROLMEN	DATE OF (
VIJAYA	837224	1	12.07	
SAMPATH	025401B	1	12.07	6.08
VISALAKSHI	945129C	1	12.07	6.08
SUBRAMANIAM	577102B	2	7.07	
ARUMUGAM	014000D	1	12.07	
JEYARAMAN	025401B	1	10.07	4.08
VENNILA	286914C	2	12.07	
BERNADETTE	840378	1	12.07	6.08
JEYAGOPI	482993C	2	11.07	
VASANTHA	125005D	2	10.07	4.08
SUNDARESAN	540718B	1	12.07	
VACCHALA	153177D	1	12.07	
ACHUTHAN	796825C	1	11.07	
THAYYAN	176669C	1	11.07	
THIRUPURAMMA	469978A	1	7.07	
SELVARAJ	23168	1	11.07	
NAVANEETHAM	104448D	1	11.07	6.08
PONNACHI	130078B	1	11.07	
ARUGADAN	156150C	1	11.07	
SRI RAMULU	128978B	1	11.07	
ARUMUGAM	14000	2	11.07	12.07,04.08
THARABAI	014674D	1	11.07	
PARIMALA	385455	2	11.07	
SULAIMAN	183183C	1	12.07	
CHANDRASEKHAR	236770	1	9.07	
RAJAMMA	395691	1	12.07	
PONNAIYAN	223274A	1	12.07	
NISAR AHMED	334967C	1	9.07	
RAJENDRAN	734410C	2	11.07	4.08
BASHEER AHMED	993015B	2	12.07	7.08
CHANDRASEKHAR	162606D	2	11.07	1.08
ISRAEL	814213A	2	9.07	
SAMBANDAN	448737C	1	7.07	
PRAKASAM	271337	1	7.07	4.07
RAJENDRAN	027890D	1	11.07	
SYED NIZAR	608308B	1	11.07	
CHAKARAI	674733C	2	11.07	
KUMARAVEL	950439B	2	11.07	6.08
EKAMBARAM	473217C	2	7.07	
LAKSHMI	137631D	2	9.07	
PACHAIYAMMAL	907093C	1	9.07	
ANANDAN	185416D	1	9.07	
NIRMALA	159093C	1	11.07	
UBAYADULLAH	978104C	1	11.07	
NATARAJAN	778053C	2	11.07	
ARJUNAN	142171D	2	7.07	11.07
LILLY MUNISAMY	038174D	1	11.07	
FAKKURUDIAN	436762C	2	11.07	12.07
MUTHUMANICKAM	137964D	2	11.07	
MOORTHY	026920C	1	11.07	

ABDUL RASHID	164653D	2	10.07	1.08
PUGHAZHENDI	555084A	1	12.07	
SEETHARAMAN	230643	1	8.07	
JAYALAXMI	767856C	2	9.07	
SHAKUNTALA	951834B	1	9.07	
EKAMBARAM	281711C	2	11.07	4.08
MANI K	169009D	2	9.07	1.08
PARVATHY	658927C	2	9.07	3.08
RAJA D	354426C	2	7.07	12.07
ARJUNAN V	143120D	2	7.07	11.07
GOVINDAN	143220D	2	7.07	12.07
SUSHEELA	669944C	1	12.07	
RAJAGOPAL	975657C	2	9.07	1.08
GNANA WILSON	647508C	2	7.07	12.07
PADMANABHAN	675256C	2	9.07	12.07
SHANTA	32`549B	2	10.07	11.07
CHANDRASEKHAR	162600D	2	10.07	1.08
ANANDAN	143114D	2	7.07	11.07
MURALIDHARAN	196144D	2	7.07	3.08
DURAIRAJ	194029D	2	7.07	2.08
ARUNACHALAM	259653	2	8.07	1.08
SARADHA	545057	2	12.07	7.08
MERCY	676760A	2	10.07	1.08
RAMAJEYAM	160703D	2	12.07	3.08
SUBRAMANIAM	775293C	2	7.07	2.08
SARADHA	545068B	1	10.07	
ESWARAN	266508C	2	7.07	2.08
BHAGAVAN DASS	567128B	2	8.07	12.07
AMMENI G	184018D	2	1.08	5.08
VIJAYA	799272C	2	10.07	3.08
KANNIAPPAN	965948C	1	8.07	4.08
JEYAKUMAR	811858A	1	11.07	
BALA	923585	1	1.08	5.08
RANGANATHAN	445936C	1	10.07	
DURAI	166215D	2	1.08	
VENKATCHALPATHI	466673	2	10.07	11.07
SURESH	048164D	1	7.07	
PATTAMMAL	577305A	2	7.07	1.08
POWN DEVARAJ	152145D	2	7.07	12.07
VINCENT	186166	1	9.07	3.08
MOSES	223517	1	7.07	2.08
PAWNAMMAL	061526D	1	9.07	
GOWRIAMMAL	199735B	1	9.07	
MURUGESAN	516817B	1	1.08	
KRISHNAVENI	497459A	2	9.07	
VEERABADRAN	312693B	2	12.07	5.08
PARVATHI	404601C	1	8.07	
KASTHURI	563581A	2	12.07	
KRISHNAMOORTHY	626051C	2	10.07	
NAVANEETHAM	156002C	2	12.07	
PONNUSAMY	252152	1	11.07	

DEVARAJ	208104D	1	12.07	
VENKATESAN	221465D	1	12.07	
SUBRAMANIAM	162948C	1	12.07	
LAKSHMI	927824B	2	8.07	
SESHALAM	303288B	2	11.07	
RAJAMMA	168069D	1	1.08	
RAMBAI AMMAL	341386B	2	7.07	
RAHIMUNISA	683677B	2	9.07	
RADHA.P	521703C	2	11.07	
BANU	130333D	2	10.07	
VELAUDHAM	722875B	1	8.07	
GAJENDRAN	116738C	2	9.07	
KANNAMMAL	971985C	2	10.07	
KANNAGOUNDER	504278C	2	9.07	
GANESAN	331892	1	10.07	
RAJAMANI	672261C	2	8.07	5.08
KUPPAMMA	976712C	2	9.07	
PANNEER.V	354600C	2	10.07	
YESTHER	107564	2	7.07	
EDWAD JONES	41555	2	7.07	
KUPPAMMA	405531C	2	10.07	
NICKELSEN	781095C	2	8.07	
VEERAMANI	893209C	1	10.07	
BOMMI	651222A	2	11.07	
GOVINDASAMY	608645A	2	7.07	
BOOPALAN	399530	1	7.07	
GRACE PUNITHA	493374C	2	8.07	
NAGARAJAPILLAI	701245A	1	9.07	
ATTODIL	604152A	1	12.07	
DURAIKRISHNAN	448394B	1	7.07	
DHANAM	506921	2	7.07	
PATTAMMAL	965974C	2	9.07	
KANNIAMMAL	100375D	2	9.07	
MAHMATH BASHA	489916C	2	8.07	
JEBAKANI	374234A	1	9.07	
PONNUSAMY	647124C	1	7.07	
MUNIAMMAL	211913D	2	12.07	5.08
SIVABHUSHANAM	125340	1	8.07	
SUSHEELA	381655B	1	12.07	
ANWAR BASHA	148845D	1	1.08	
MANGALAXMI	416256C	1	12.07	
PALANIVEL	190072D	2	12.07	
DEVANESAN	974929C	1	7.07	
NATARAJAN	930576C	1	7.07	
BABU	943459B	1	7.07	3.08
LAKSMANAN	918487C	1	10.07	
VISHWANATHAN	289426C	1	8.07	
LAKSHMI	564992C	1	11.07	
YESUPATHAM	597344C	1	8.07	
MOHAN N	466870C	1	12.07	
SAROJA	881319C	1	12.07	6.08

KANNAYAN	305295B	1	12.07	
SUBRAMANIAM	598650B	1	12.07	
VELU	208812D	1	12.07	
THAVAMANI	903218C	1	12.07	5.08
JAYACHANDRAN	797222B	1	11.07	
GEETHESWARI	753666B	1	9.07	
ARPUTHAM	703827A	1	7.07	
JANARDHANAM	296975B	1	8.07	11.07

OUTCOME	OUTCOME	TIME TO OUTCOME		PRESENT	Jul-07	Aug-07	Sep-07	Oct-07
		6		1				
		5	6	2				
		5	6	2				
		6		1	6	6	6	6
		6		1				
		1	7	2				6
		6		1				
		5	6	2				
		6		1				
		5	6	2				6
		6		1				
		6		1				
		6		1				
		6		1				
		6		1	6	6	6	6
		6		1				
		7	7	2				
		6		1				
		6		1				
		6		1				
8	5,5		1	2				
		6		1				
		6		1				
		6		1				
		6		1			6	6
		6		1				
		6		1				
		6		1			6	6
		5	5	2				
		1	7	2				
		8	2	2				
		6		1			6	6
		6		1	6	6	6	6
		1	9	2	6	6	6	6
		6		1				
		6		1				
		6		1				
		1	7	2				
		6		1	6	6	6	6
		6		1			6	6
		6		1			6	6
		6		1			6	6
		6		1				
		6		1				
		6		1				
	5,7,8		4	2	6	6	6	6
		6		1				
		7	1	2				
		6		1				
		6		1				

7,8		3	2				6
	6		1				
	6		1			6	6
	6		1			6	6
	6		1			6	6
	1	5	2				
	5	4	2			6	6
	5	6	2			6	6
	5	5	2	6	6	6	6
	5	4	2	6	6	6	6
1,8		5	2	6	6	6	6
	6		1				
	5	4	2			6	6
	5	5	2	6	6	6	6
	5	5	2			6	6
	5	4	2				6
	5	3	2				6
1,8		4	2	6	6	6	6
	5	8	2	6	6	6	6
	5	7	2	6	6	6	6
	5	5	2		6	6	6
	1	7	2				
	1	3	2				6
	5	4	2				
	5	7	2	6	6	6	6
	6		1				6
	5	7	2	6	6	6	6
	5	4	2		6	6	6
	5	4	2				
	5	5	2				6
5,8		8	2		6	6	6
	6		1				
	7	4	2				
	6		1				6
	6		1				
	5	1	2				6
	6		1	6	6	6	6
	5	6	2	6	6	6	6
5,8		5	2	6	6	6	6
	5	6	2			6	6
	5	7	2	6	6	6	6
	6		1			6	6
	6		1			6	6
	6		1				
	5	5	2				
	6		1		6	6	6
	6		1				

6 1
6 1
6 1

6 1 6
6 1 6 6
6 1 6
5 9 2 6 6 6

6 1 6 6 6 6
6 1 6 6 6 6

6 1 6

6 1 6 6 6 6
6 1 6 6 6
6 1 6 6

6 1 6 6 6 6
6 1 6 6
6 1 6 6
6 1 6 6 6
6 1 6 6

5 5 2
6 1 6 6 6

6 1
6 1

6 1 6 6 6 6
6 1 6 6 6 6
5 8 2 6 6 6 6
6 1 6
6 1 6 6 6
6 1
6 1 6 6 6
6 1
7 6 2

6		1				
6		1				
6		1				
5	5	2				
6		1				
6		1			6	6
6		1	6	6	6	6
5	3	2		6	6	6

Nov-07	Dec-07	Jan-08	Feb-08	Mar-08	Apr-08	May-08	Jun-08	Jul-08
		6	6	6	6	6	6	6
	6	6	6	6	6	6	5	6
	6	6	6	6	6	6	5	6
6	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
6	6	6	6	6	1	6	6	6
	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	5	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	1	6	6	6
	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	7	
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	5	6	6	6	5	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	5	6	6	6
	6	6	6	6	6	6	6	1
6	6	8	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	1	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	1	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
5,7,8								
6	6	6	6	6	6	6	6	6
6	7							
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6

6	6 7,8							
	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	1	6	6	6
6	6	5	6	6	6	6	6	6
6	6	6	6	5	6	6		6
6	5	6	6	6	6	6	6	6
5	6	6	6	6	6	6	6	6
6 1,8		6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
6	6	5	6	6	6	6	6	6
6	5	6	6	6	6	6	6	6
6	5	6	6	6	6	6	6	6
5	6	6	6	6	6	6	6	6
6	6	5	6	6	6	6	6	6
1,8		6	6	6	6	6	6	6
6	6	6	6	5	6	6	6	6
6	6	6	5	6	6	6	6	6
6	6	5	6	6	6	6	6	6
	6	6	6	6	6	6	6	1
6	6	1	6	6	6	6	6	6
	6	6	6	5	6	6	6	6
6	6	6	5	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	5	6	6	6	6	6
6	5	6	6	6	6	6	6	6
			6	6	6	5	6	6
6	6	6	6	5	6	6	6	6
6	6	6	6	6 5,8		6	6	6
6	6	6	6	6	6	6	6	6
		6	6	6	6	5	6	6
6	6	6	6	6	6	6	6	6
		6	6	6	6	6	6	6
5	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	5	6	6	6	6	6	6
6 5,8		6	6	6	6	6	6	6
6	6	6	6	5	6	6	6	6
6	6	6	5	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
			6	6	6	6	6	6
	6	6	6	6	6	5	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6

6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6

6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 5 6 6

6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6

6 6 6 6 6 6 6 6 6

6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6

6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6

6 6 6 6 6 6 5 6 6
6 6 6 6 6 6 6 6 6

6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6

6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 5 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 6 6
6 6 6 6 6 6 6 7

	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
	6	6	6	6	6	6	6	6
	6	6	6	6	6	5	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
6	6	6	6	6	6	6	6	6
5	6	6	6	6	6	6	6	6

Aug-08
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6

6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6
6

6
6

6

6
6
6

6
6
6
6

6
6

6

6
6
6

6
6
6
6
6

6
6

6
6

6
6
6
6
6
6
6
6

6
6
6
6
6
6
6
6
6