RISK FACTORS FOR MORTALITY IN PATIENTS WITH INVASIVE PNEUMOCOCCAL DISEASE IN SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences,
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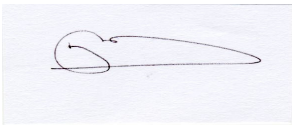
in partial fulfillment of the requirements for the degree of
Master of Science (Med) in Epidemiology & Biostatistics.

DECLARATION

I declare that this research report is my own, unaided work. It is being submitted in partial fulfillment of the requirements for the Degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.



Peter Suwirakwenda Nyasulu 24 August 2007

ABSTRACT

Introduction

Invasive pneumococcal disease (IPD) is an important cause of morbidity and mortality in many parts of the world. It is estimated that pneumococcal disease causes more than one million-childhood deaths every year and the burden of disease is greater in developing countries. The main aim of this study was to analyze risk factors associated with mortality in invasive pneumococcal disease in all ages in South Africa.

Materials and Methods

We performed an analytical cross-sectional analysis of secondary data from national population-based surveillance for invasive *Streptococcus pneumoniae* infection in South Africa. The study period was 1 January 2003 to 31 December 2005, and the mortality analysis used a subset of laboratory-confirmed cases who had a completed case report form and available mortality data. Multiple logistic regression models were constructed to identify risk factors significantly associated with the increased risk of death in patients with invasive pneumococcal disease. Separate models were used to evaluate risk factors for death in patients with meningitis and those with other IPD.

Results

There were 1154 (24%) cases of *Streptococcus pneumoniae* meningitis and 3736 (76%) cases of other invasive disease. The overall case fatality rate was 1360/4890 (27.8%) of which 911 (67%) patients died within 2 days of admission and 449 (33%) died between 2 days and 30 days of admission.

Variables associated with mortality in a logistic regression analysis of all IPD patients included meningitis (OR 2.8, CI 1.9 – 3.9, P=<0.001), HIV-infection (OR 2.8, CI 1.6 – 4.6, P=<0.001), acute severe illness measured by Pitt bacteraemia score >=4 (OR 4.7, CI 2.8 – 7.7, P=<0.001) and prior antibiotic use within 2 months

before first positive culture (OR 2.1, CI 1.4 – 3.1, P=<0.001). In addition to this children less than 1 year and adults ≥45 years were more likely to die compared to other age groups. Patients from Western Cape Province were significantly less likely to die (OR 0.27, CI 0.15 – 0.50, P=<0.001) compared to other provinces.

Amongst HIV-positive patients severe immunosuppression (low CD4+ count) was a risk factor for death. Risk factors for death were similar in patients with other IPD and meningitis except for HIV which was associated with death in the meningitis group but not in the other IPD group. Antibiotic resistance and vaccine-serotype disease were not associated with increased risk of death.

Discussion and Conclusions

IPD is associated with a high mortality in South Africa. Our findings of increased risk of death in HIV-positive patients especially those with low CD4+ count are of importance given the high prevalence of HIV amongst patients with IPD. Introduction of the pneumococcal conjugate vaccine as part of the national expanded program for immunization (EPI) and ensuring access to antiretroviral therapy for HIV-positive patients where indicated should be prioritized.

DEDICATION

I dedicate this work to my loving grandparents who raised me up from the age of 1 year and taught me the beauty of education and the love of Christ.

Reverend Petros Suwirakwenda Nyasulu 1908-1980

And

Bessie Nyaharawa 1914-1991

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Finally, I thank my wife Juliet and my children Angella and Wanangwa for being a constant source of love, inspiration and encouragement. May the Lord bless them.

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ABBREVIATIONS

ART-Antiretroviral therapy

CD-Cluster of differentiation

CFR-Case fatality rate

CI-95% Confidence interval

CLSI-Clinical and Laboratory Standards Institute

CRFs-Case report forms

CSF-Cerebrospinal fluid

ELISA-Enzyme-linked immunosorbent assay

HIV-Human Immunodeficiency Virus

IPD-Invasive pneumococcal disease

MIC-Minimum inhibitory concentration

NICD-National Institute for Communicable Diseases, Johannesburg

OR-Odds ratio

PCV7-7-valent pneumococcal conjugate vaccine

RMPRU-Respiratory & Meningeal Pathogens Research Unit

SSI-Staaten Serum Institute

USA-United States of America

WHO-World Health Organization

CHAPTER 1

General Introduction

This chapter gives an overview of the burden of invasive pneumococcal disease and why it is an important public health problem. The chapter also contains a statement of the problem, justification for the study, objectives of the study and a literature review from relevant publications.

1.1 Background

Invasive S*treptococcus pneumoniae* infection is an important cause of morbidity and mortality in many parts of the world.(1-4) The most common risk groups are children under 2 years, those older than 65 years and people with underlying immunodeficiency such as human immunodeficiency virus (HIV) infection.(1;2;5) HIV seroprevalence in South Africa is >20% in people of age 15-49 years which means that more people are prone to invasive *S. pneumoniae* infections.(4;6-8) Increasing resistance to antimicrobials is an additional concern.(4;6;7;9)

The National Institute for Communicable Diseases (NICD) Respiratory and Meningeal Pathogens Research Unit (RMPRU) has been conducting national laboratory-based surveillance for invasive pneumococcal disease (IPD) in South Africa since 2000. Objectives of the surveillance system include obtaining a more precise national estimate of the burden of IPD, monitoring trends of emerging antibiotic resistance as well as monitoring the association between IPD and HIV infection in this population. Information is provided to clinicians and public health specialists for appropriate utilization.

1.2 Statement of the problem

HIV infection has compounded the already existing health burdens in many low and middle-income countries including South Africa.(1-4) Many studies have shown that HIV is a major risk factor for IPD, which has a high case fatality rate of up to

21.6% in those with underlying HIV.(1-4;7) Other studies have even reported death rates of 28% in patients with invasive pneumococcal pneumonia.(10) However HIV infection has not been shown to be a risk factor for mortality in patients with pneumococcal bacteraemia. To our knowledge there have been no studies evaluating HIV as a risk factor for mortality in patients with pneumococcal meningitis.

Many studies have also shown increasing prevalence of paediatric serotypes/serogroups in the HIV-positive adult population and these strains are commonly associated with penicillin resistance.(5-9) Penicillin resistance has not been shown to be associated with increased risk of mortality. Increasing levels of microbial resistance to penicillin, the first line treatment for pneumococcal disease, have been reported across the globe with occasional resistance to extended spectrum antibiotics i.e. cephalosporins.(11;12)

South Africa has one of the highest reported rates of penicillin resistance and reported the first resistant isolates in 1977/8.(1;2) Due to selective pressure, additional classes of antibiotics in common use such as macrolides, cotrimoxazole and chloramphenicol may select resistance additional to penicillin resistance.(11) This scenario complicates control measures and clinical decision-making in the management of IPD in low and middle-income countries like South Africa, as alternative antibiotics like third-generation cephalosporins are expensive.

Most of the commonly reported resistant serotypes are well covered by the 7-valent pneumococcal conjugate vaccine (PCV7),(13;14) which unfortunately is not accessible to many low and middle-income countries. Studies in United States of America (USA), Canada and Australia have shown a significant decline in the prevalence of penicillin resistance following vaccine introduction.(9;13;14) These studies have also shown a decline in the prevalence of IPD in both vaccinated and unvaccinated populations since the vaccine was introduced for widespread use. The indirect effect is thought to be due to herd immunity.(9;13;14) Whether penicillin

resistance, vaccine-serotype disease and HIV infection are associated with mortality in patients with IPD has not been clearly demonstrated.

1.3 Justification

There have been no studies done to identify the risk factors for mortality due to IPD in South Africa on a national level. This data would be useful in planning targeted public health interventions to control IPD.

1.4 Literature Review

1.4.1 Overview of studies evaluating risk factors for pneumococcal mortality

Pneumonia is the leading infectious cause of death in both children and adults. It is estimated that pneumococcal disease causes more than one million childhood deaths every year and the burden of disease is greater in developing countries.(2;15) Mortality from invasive pneumococcal disease ranges from 2.8% in uncomplicated cases to 58% in pneumococcal meningitis cases.(2;5;11;16;17)

Previous studies have looked at risk factors associated with death in patients with pneumococcal bacteraemia. Rondon et al. in Madrid, Spain found that low white cell count less than 10,000/cubic mm; acidosis; respiratory symptoms or signs (tachypnoea, chest pain, wheezing); neurological findings (altered consciousness) were associated with death, but found no association between HIV infection, antibiotic resistance and death.(17)

Feikin et al. observed that there was no increased mortality from bacteraemic pneumococcal pneumonia among patients with HIV infection.(18) Turett et al. in New York, USA found that severity of the illness (odds ratio [OR] 33.8, P<0.001); multilobar infiltrates and/or effusion (OR 2.4; P=<0.02); Hispanic ethnicity (0R 2.4, P=<0.02); age (P=<0.02) and high-level penicillin resistance (OR 6.0; P<0.02) were significantly associated with death.(16) This is the first study that reports penicillin resistance as an independent risk predictor of death among pneumococcal bacteraemia patients. In Johannesburg, South Africa, Feldman et al. also showed

severity of illness as a predictor of mortality in bacteraemic pneumococcal pneumonia.(3)

We evaluated whether pneumococcal resistance to penicillin, HIV infection and childhood pneumococcal serotypes/serogroups were associated with increased mortality among patients with invasive pneumococcal disease. These data may contribute to our understanding of how universal vaccination for pneumococcus would impact on disease in South Africa.

1.4.2 Childhood Serotypes/Serogroups

Childhood *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, 23F are a major cause of IPD in children and are normally carried in the nasopharynx of young children. This makes daycare centers, orphanages etc conducive environments for transmission of *S. pneumoniae* among children, at the same time exposes adult caretakers to the risk of acquiring infection. It has been shown that there is an increase in the prevalence of IPD in adults caused by childhood serotypes(1;2) and the frequency of occurrence was more in women compared to men (47% vs. 21%, P=0.01).(3;6)

Pneumococcal conjugate vaccine has been shown to be effective in reducing pneumococcal carriage. The efficacy of this vaccine (PCV7) in reducing IPD burden has been shown by studies done in USA, Canada, Australia, Western Europe and other parts of the world.(13;14;19;20) Even though the burden of invasive disease is increasing due to childhood serotypes, no study to date has looked at the impact of childhood serotypes on mortality in patients with IPD in South Africa.

1.4.3 HIV Infection

HIV infection has been shown to be a major risk factor for IPD in Africa and other parts of the world. In South Africa increasing prevalence of HIV has had an impact on occurrence of IPD with more cases occurring in HIV-seropositive individuals as compared to HIV-seronegative individuals.(1;2) Madhi et al. found that among

children the overall burden of IPD was 41.7 times higher (confidence interval (CI) 26.5-65.6) in HIV-infected compared with HIV-uninfected children.(8) Similar findings were also shown by Jones et al who reported a 36.9 fold increase in IPD among HIV-seropositive compared to HIV-seronegative children and 8.2 fold increase in IPD among HIV-seropositive adults compared to HIV-seronegative adults.(4)

Crewe-Brown et al. demonstrated a significant difference in the proportion of paediatric serotypes among the HIV-seropositive compared to HIV-seronegative patients with IPD (37.0% vs. 25.4%) (OR 1.73, CI 0.98-3.05, P=0.04).(7) HIV-seroprevalence could therefore explain why childhood serotypes are commonly causing IPD in adults. However HIV infection has not been clearly shown to be a risk factor for death in patients with IPD.(2-4;8;10;16)

1.4.4 Penicillin Resistance

Penicillin resistance has been increasing at an alarming rate partly because of injudicious use of antibiotics. The highest reported rates of resistance in South Africa have been 39.4% among cases of IPD in a study done in 1996/97. In that study penicillin non-susceptible isolates increased from 35.5% as observed in 1986/87.(1;16)

Antimicrobial resistance in the pneumococcus has been shown to be higher in children compared to adults.(6;7) and that women compared to men harbor more penicillin non-susceptible isolates (15% versus 1%, P=0.008) including cotrimoxazole resistant isolates (21% versus 5%, P=0.016).(3) Childhood serotypes/serogroups have been associated with penicillin resistance and also resistance to other antibiotics.(6) Since childhood serotypes occur more in women than men, this could be the reason why women harbor more penicillin non-susceptible isolates than men.(8)

An association between antibiotic resistance and HIV seropositivity was shown among adult patients: 19% of isolates in the HIV-positive patients were penicillin resistant compared to 4.25% in the HIV-negative patients (OR 5.25, CI 2.25-12.45, P=<0.001).(7) This association was more significant in children where 53.3% of the isolates in HIV- positive and 30.2% of the isolates in HIV- negative patients were resistant to penicillin.(7) However many previous reports have not documented increased mortality in patients with penicillin-resistant isolates.(1-8;10;16)

One study in the USA that reported an association with mortality has been highlighted above.(16) Therefore data are lacking on risk factors for mortality due to invasive pneumococcal disease at national level. This study was therefore undertaken to determine risk factors for mortality in patients with invasive pneumococcal disease in South Africa.

1.5 Objectives

1. To describe risk factors for mortality in the population of laboratory-confirmed invasive pneumococcal disease patients of all age groups in South Africa.

Specific exposures of interest included:

- Antibiotic susceptibility and non-susceptibility to penicillin.
- Vaccine type and non-vaccine type disease.
- HIV-seropositive and HIV-seronegative patients.
- Meningitis and other invasive pneumococcal disease.

2. To determine risk factors for death in patients with meningitis and those with other IPD

CHAPTER 2

Materials and Methods

In this chapter study population, data sources and data management are discussed. Definitions of variables, study hypotheses as well as statistical methods and data analyses are stated.

2.1 Study Design

This was an analytical cross-sectional analysis of secondary data from national, population-based surveillance for IPD in South Africa. The study period was 1 January 2003 to 31 December 2005 and data were collected from eight of the nine provinces. The analysis used a subset of the surveillance data from enhanced surveillance sites with completed case report forms (CRFs) and data on outcome.

2.2 Hypothesis

We hypothesized that age of the patient, HIV infection, vaccine-serotype disease and penicillin resistance were independent risk factors for mortality in patients with IPD in South Africa and that risk factors might differ for meningitis and other IPD.

2.3. Surveillance for Invasive Pneumococcal Infection.

The Respiratory and Meningeal Pathogens Research Unit (RMPRU) of the NICD performed laboratory-based surveillance for invasive pneumococcal infections. The surveillance system defined invasive infection as isolation of pneumococcus from a normally sterile site (e.g. blood, CSF, peritoneal fluid, pleural fluid and joint fluid). All clinical laboratories in South Africa were encouraged to send isolates of pneumococci to the RMPRU reference laboratory. Here culture, antimicrobial susceptibility testing and serotyping were done on each isolate that had been received.(21;22)

The surveillance system established enhanced sites in 8 of the 9 provinces in order to obtain more detailed epidemiologic data on patients from those sites. Gauteng

and KwaZulu Natal Provinces had 4 sites each, Mpumalanga and Western Cape had 3 sites each, Limpopo and Free State had 2 sites each, and Eastern Cape and North West had 1 site each (Appendix 1). In addition to laboratory reinforcement, surveillance officers who were qualified nurses were placed at each of these hospitals to collect data from cases admitted to these hospitals with a laboratory diagnosis of invasive pneumococcal disease. Using standardized case report forms (Appendix 3); they collected data on demographic, clinical and microbiologic characteristics as well as clinical outcomes on each case. These data were abstracted from hospital records and through interview with individual patients or their proxy.

For patients without HIV test result, the surveillance officers carried out a pre-test and post-test counseling and document HIV test results in the case report forms. Therefore, data from enhanced sites were more complete on outcome since the surveillance officers follow up these patients from admission to outcome. Our study focused on a subset of the data from enhanced surveillance sites in order to examine risk factors for mortality.

2.4 Study Population and sampling

This 3-year study included records of all cases of invasive pneumococcal disease from enhanced surveillance sites reported to NICD. The mortality analysis was restricted to a subset of laboratory-confirmed IPD cases i.e. those who had a completed CRF with available mortality data.

Preliminary analysis was done to compare patients included in the mortality risk factor analysis to the overall IPD population to ascertain comparability of the two groups. Additional separate analyses were done to evaluate risk factors for death in the population of cases with confirmed meningitis and those with other IPD. Another separate analysis was done to assess the influence of low CD4+ count on mortality in a population of IPD patients with HIV co-infection.

2.5 Data management

The pneumococcal surveillance data for 2003-2005 were entered in EPI info Version 6.04d computer software package (Centers for Disease Control and Prevention, Atlanta, Georgia) by a team of data entry clerks at RMPRU and exported into a Microsoft Excel spreadsheet workbook. Validity of the data was done by checking the database for completeness of the records and identification of errors on data entry. This was done by verifying approximately 10% of the records in the database with records as they appeared on the case report forms. Mostly demographic and clinical data were verified. This helped to assess consistency of records entered with data on case report forms.(23) Identified errors were corrected on the database.

Inconsistent laboratory data for CD4+ count and viral load was also verified using the computerised laboratory database. All variables of interest were then recoded for analysis such that most variables then became dichotomous. Cross tabulations and frequency tables were done to ascertain internal consistency of the data. Missing data were excluded from the analysis. Most of these validity checks were done using Excel software package and data were thereafter exported into Stata software, version 9.0 for analysis.

2.6 Definitions

All definitions of study variables were established before data were analyzed.

2.6.1 Main exposures of interest

- Invasive pneumococcal disease was defined as presence of a pneumococcal isolate from a normally sterile site, such as blood, cerebrospinal fluid (CSF), pleural fluid, peritoneal fluid and joint fluid in a patient admitted to hospital.(18)
- IPD clinical syndrome was defined as (i) Meningitis: isolation of pneumococcus from CSF. (ii) Bacteraemia: isolation of pneumococcus from blood (pneumonia and bacteraemia without focus). (iii) Other invasive

disease: isolation of pneumococcus from other sterile sites i.e. joint aspirate, peritoneal fluid and pleural fluid.

- Age at last birthday in complete years on the day specimen was collected.
- Vaccine-serotype disease was defined as IPD caused by pneumococcal serotypes found in the 7-valent pneumococcal conjugate vaccine. These are serotype/serogroup 4, 6B, 9V, 14, 18C, 19F and 23F.(13)
- Antibiotic susceptibility for penicillin was defined as 'non-susceptible' referring to intermediate resistance or resistance (MIC>0.06 μg/ml) and 'susceptible' referring to antibiotic susceptibility (MIC≤0.06 μg/ml).(24) All antibiotics were evaluated (penicillin, ceftriaxone, erythromycin, cotrimoxazole, clindamycin, chloramphenicol and rifampicin) but penicillin was the main exposure because it is the main drug of choice.
- HIV status was defined as presence of a positive or negative ELISA test (enzyme-linked immunosorbent assay) result.(6)

2.6.2 Other exposures evaluated

- Nosocomial infection was defined as invasive pneumococcal disease occurring more than 2 days after the patient was admitted to hospital.
- Acute severe illness was defined as a Pitt bacteraemia score equal to or greater than 4 at the time of the positive blood/CSF. This score is used to measure severity of disease in bacteraemia but was used in meningitis patients as a measure of generalized sepsis

  The Pitt bacteraemia score was assessed using the following parameters:

  (i) Oral temperature: 2 points for a temperature of ≤35ºC or ≥40ºC, 1 point for temperature of 35.1ºC-36.0ºC or 39.0ºC–39.9ºC and 0 point for temperature of 36.1ºC-38.9ºC.

  (ii) Hypotension: 2 points for systolic blood pressure of less than 90 mm Hg.

  (iii) 2 points for receipt of mechanical ventilation

  (iv) 4 points for cardiac arrest

(v) Mental status: if alert 0 point; disoriented 1 point; stuporous 2 points and comatose 4 points.(25;26)

- Underlying illness associated with immunosuppression was defined as the presence of malignancy, asplenia, autoimmune condition, organ transplant or receipt of immunosuppressive agents e.g. prednisolone or other cytotoxic drugs. Other underlying medical condition were defined as presence of tuberculosis, diabetes mellitus, cirrhosis / liver failure, chronic renal failure, heart disease, asthma, malnutrition, severe burns, severe trauma and head injury.(27)
- Prior antibiotic use within 24 hours was defined as use of any antibiotic less than or equal to 24 hours before the first positive blood/CSF culture.(25-27)
- Prior antibiotics use within the past 2 months was defined as use of any antibiotic other than cotrimoxazole prophylaxis within the 2 months preceding the first positive blood/CSF culture.(25-27)
- Cotrimoxazole prophylaxis was defined as regular use of cotrimoxazole for purposes of *Pneumocystis jiroveci* pneumonia prophylaxis in HIV-sero positive patients.
- Low CD4+ count was defined as CD4+ absolute value indicative of severe immune deficiency in HIV co-infection as shown below (Table 2.1).

Table 2.1: CD4 + criteria for severe HIV immunodeficiency

Immunological markers	Age-specific recommendation to initiate ART[a]			
	≤11 months	12-35months	36-59months	≥5years
%CD4+[b]	<25%	<20%	<15%	<15%
CD4 count[b]	<1500cells/mm^3	<750 cells/mm^3	<350cells/mm^3	<200cells/mm^3

[a] Cut off levels for initiating antiretroviral therapy (ART). CD4+ drop below these levels significantly increases the risk of disease progression and death.

[b] CD4+% is the preferred measure for children <5 years old.

(The table has been adapted from 'Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access', WHO 2006.(28))

- Gender was defined as either male or female sex.
- Alcohol abuse was defined as self report of alcohol abuse or not.
- Smoking status was defined as "current smoker" or "does not smoke".
- Province was defined as one of the nine provinces in South Africa in which the patient presented to hospital.
- Race was defined as black, coloured, white or Indian origin.

2.6.3. Outcome

The outcome of interest was mortality defined as death within 30 days of admission after the first positive blood/CSF culture result for S *pneumoniae* was obtained. Patients who were discharged from hospital within or after 30 days were considered to have survived the episode. To minimize misclassification of deaths that may have occurred due to causes other than pneumococcal infection, all deaths occurring after 30 days were excluded from the analysis. Those with missing data on outcome and date of death were also excluded.(18)

2.7 Laboratory methods

2.7.1 Antibiotic susceptibility testing

Susceptibility testing for penicillin, rifampicin, trimethoprim/sulphamethoxazole, erythromycin, clindamycin, chloramphenicol and tetracycline was determined by the disk diffusion method.(24) Minimum inhibitory concentrations (MIC) were confirmed by agar dilution for penicillin and ceftriaxone, and by Etest (AB Biodisk, Solna, Sweden) for all the other antimicrobials. CLSI breakpoints for meningitis were used for ceftriaxone. For penicillin the term 'non-susceptible' referred to intermediate resistance or resistance (MIC>0.06 μg/ml) and the term 'susceptible' referred to antibiotic susceptibility when MIC≤0.06 μg/ml. For all other antibiotics,

isolates were categorised as “non-susceptible” referring to intermediate resistance and resistance, or “susceptible”, according to Clinical and Laboratory Standards Institute (CLSI) guidelines (24).

2.7.2 Pneumococcal Serotyping

All pneumococcal isolates were serotyped by capsular swelling (Quellung reaction) using sera from the Staaten Serum Institute (SSI), Copenhagen, Denmark.

2.7.3 HIV testing

This was done by using enzyme-linked immunosorbent assay (ELISA). A positive HIV test result referred to a positive serum reaction to ELISA test.(6) Two HIV ELISA tests were used: Determine HIV-1/2 (Abbott GmbH) and Murex HIV 1+2 (Murex Diagnostic Limited).

2.8 Statistical methods and Data analysis

Statistical analysis was done using Stata statistical software, version 9.0 (Stata Corp.2005. College Station, Texas). The chi-squared test was used to compare differences in characteristics between categorical variables (e.g. demographic and microbiologic characteristics of cases from enhanced surveillance and non enhanced surveillance sites). Continuous variables (e.g. age, CD4+ count) were compared using Mann-Whitney U-test. Factors that were significant at $P \leq 0.1$ on univariate analysis were included in logistic regression models to assess the effects of multiple risk factors on invasive pneumococcal disease mortality.

Stepwise logistic regression employing forward selection and backward elimination.The models were also tested for goodness of fit using the Pearson X^2 and the deviance X^2. Interactions between main effects in the models were also assessed for significance and co linearity. Potential confounding variables were adjusted for in the models. Precision of estimate for odds ratio in the logistic regression models was defined as $P \leq 0.05$ significance level. All statistical tests

excluded missing values. In this study P>0.05 in the multivariate analysis was considered not statistically significant.

Incidence rates were calculated based on the number of cases reported each year from January 1 through December 31, divided by mid-year population estimates for each year supplied by Statistics South Africa (Stats SA). The incidence rates were calculated from all IPD cases reported by age and province.

Preliminary analyses were conducted to compare patients from enhanced surveillance sites (those eligible to have CRFs completed and be included in the mortality analysis) to the population of all patients with IPD. This was done because if patients from enhanced surveillance sites were very different from patients at non-enhanced sites this might affect generalizability of findings. Amongst patients presenting to enhanced surveillance sites those who had completed case report forms were compared to those without case report forms. Only patients with completed CRFs were included in the mortality analysis as mortality data was unreliable in those without CRFs.

Descriptive analysis was performed for patients with completed CRFs (i.e those included in the mortality analysis). For some of the main exposures of interest (e.g. HIV infection, meningitis versus other IPD and antibiotics in the last 2 month), exposed and unexposed groups were compared to better characterize these groups.

For the analysis of risk factors for mortality multiple models were constructed:
(i) 'The all IPD model' to evaluate risk factors for death in all IPD patients.
(ii) Separate models for meningitis and other IPD to investigate if risk factors associated with mortality were different between the two clinical syndromes.
(iii) The low CD4+ count model to evaluate if low CD4+ was a risk factor for death in IPD patients with HIV co-infection.

2.9 Ethical approval

The Postgraduate Committee and the Research Ethics Committee, Faculty of Health Sciences, University of Witwatersrand approved the study.

CHAPTER 3

Results

3.1 Overview of all IPD cases

There were 11,116 cases of IPD reported to RMPRU from 2003 to 2005.

3.2 Incidence rates of IPD

The national incidence rates of IPD were 7/100,000 for 2003, 8.2/100,000 for 2004 and 8.8/100,000 for 2005.There was an increasing trend of IPD over the study period.

The incidence rates were highest in children <1 year 49.9/100,000 persons in 2003, 63.1/100,000 persons in 2004 and 66.9/100,000 in 2005 and lowest in the young adults 15- 24 years 2.1/100,000 2003, 2.7/100,000 2004 and 2.2/100,000 for 2005. The burden of IPD was highest in Gauteng, Western Cape and Mpumalanga provinces, which also showed an increasing incidence rates over the study period (Figure 1 and Figure 2).

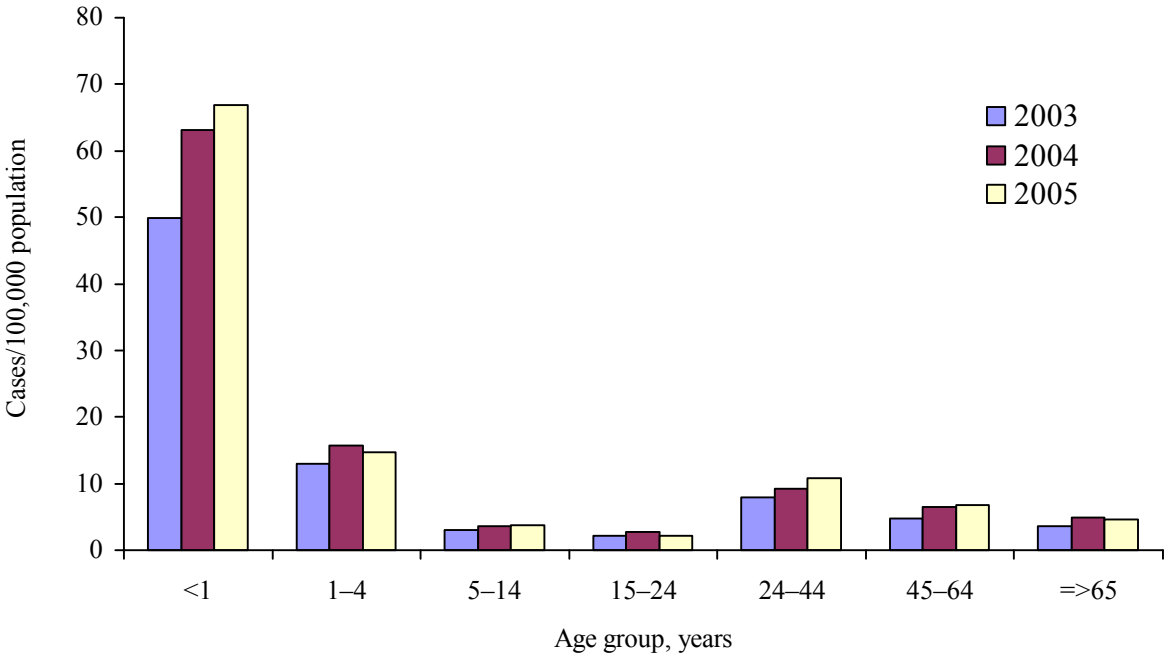

Figure 1: Age-specific annual incidence rates of invasive pneumococcal disease in South Africa by year, 2003-2005.

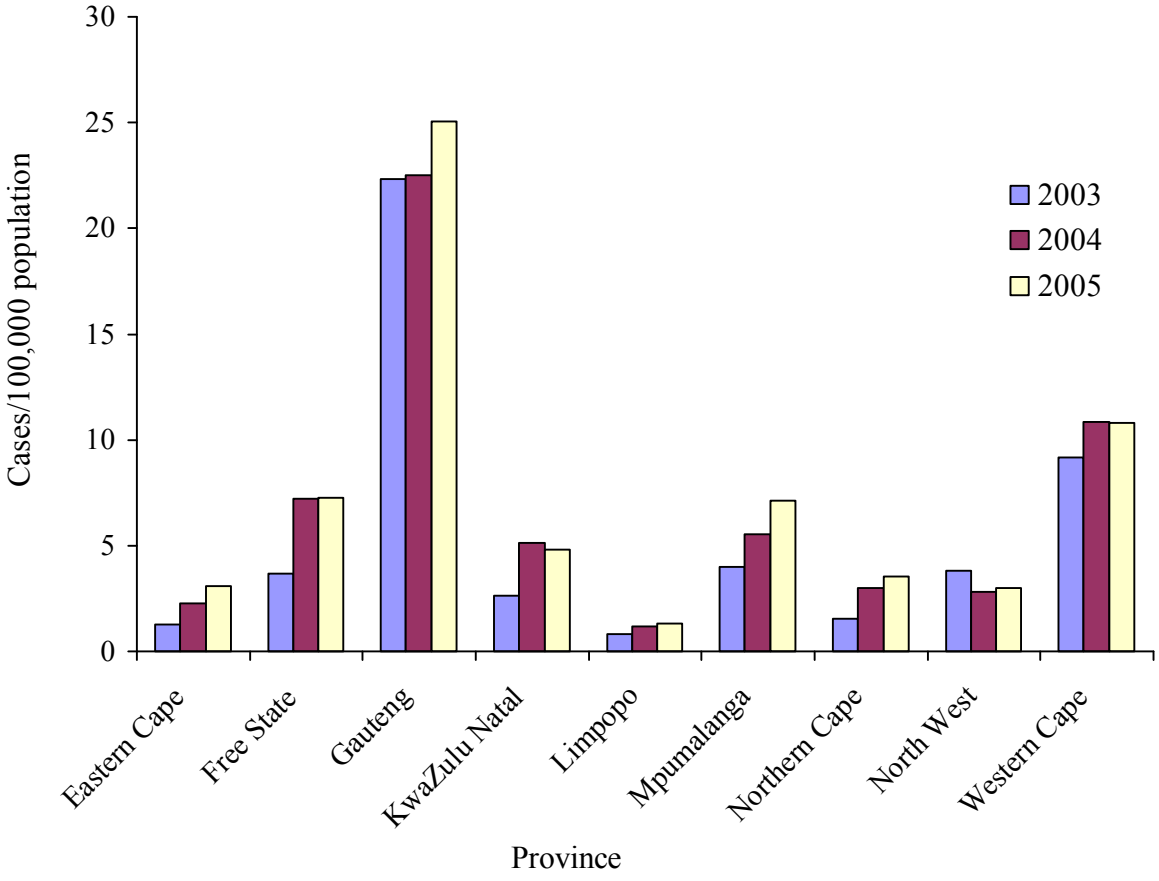

Figure 2: Annual incidence rates of invasive pneumococcal disease by province and year, 2003-2005.

3.3 Comparison of population included in mortality study to population of all IPD in South Africa

3.3.1 Comparison of cases presenting to enhanced and non-enhanced sites (Table 3.1).

6302 (56.7%) cases were reported from Gauteng Province followed by 1430 (12.9%) from Western Cape Province and 1216 (10.9%) from KwaZulu Natal Province. Northern Cape Province reported the lowest number of cases 73 (0.7%). Of the total number of cases, 6051 (54%) were from enhanced sites and 5065 (46%) were from non- enhanced sites.

There was slightly more missing data on age at non-enhanced sites (7.6% versus 4.0%). There were significant differences in the age distribution of cases from enhanced and non-enhanced sites. In the enhanced sites the burden of disease was higher in the <1 year age group 1086 (18%), the 1-4 years age group 1002 (16.6%) and the 25-44 years age group 2035 (33.6%). Distribution of cases at the non-enhanced sites showed a similar pattern with the burden being higher in the <1 year old group 764 (15.1%), the 1-4 years 758 (15.0%) and 25-44 years 1660 (32.8%). However enhanced sites reported a greater proportion of cases in these age groups compared to non-enhanced sites and this observed difference was significant (P=0.006). Gender distribution between enhanced and non-enhanced sites was not different, but there were more missing data on gender from non-enhanced sites.

Of the cases reported from enhanced sites within the study period 3422 (56.6%) were from Gauteng Province, 842 (14%) were from Western Cape Province, 934 (15.4%) were from KwaZulu Natal Province and 377 (6.2%) from Free State. There was a significant difference in proportion of cases reported between provinces comparing enhanced and non-enhanced sites (P=<0.001). There was a significant difference (P=<0.001) in the type of specimen collected between enhanced and non-enhanced sites with more blood cultures in enhanced sites: 4333 (71.6%) compared to 2866 (56.6%) in the non-enhanced sites. There was a greater proportion of CSFs

at non-enhanced sites: 1945 (38.4%) compared to 1418 (23.3%) in enhanced sites. The proportions of vaccine and non-vaccine-serotypes between enhanced and non-enhanced sites were not different (P=0.066).

The proportions of antibiotic resistance were greater in enhanced sites as compared to non-enhanced sites: penicillin (28.4% versus 26.5% P=0.03), rifampicin (5% versus 3.5% P=<0.001) and cotrimoxazole (57.9% versus 51.9% P=<0.001).

Tables 3.1: Demographic and Microbiologic Characteristics of patients with invasive pneumococcal disease from enhanced and non-enhanced sites

	Enhanced sites (n=6051)	Non-enhanced sites (n=5065)		
Characteristics	N (%)	N (%)	*X^2	P
Age group in years				
<1	1086 (18.0)	764 (15.1)		
1-4	1002 (16.6)	758 (15.0)	18.1	0.006
5-14	557 (9.2)	495 (9.8)		
15-24	351 (5.8)	310 (6.1)		
25-44	2035 (33.6)	1660 (32.8)		
45-64	621 (10.3	553 (10.9)		
≥65	152 (2.5)	139 (2.7)		
Missing	247 (4.0)	386 (7.6)		
Sex				
Male	3038 (50.2)	2497 (49.3)	0.011	0.916
Female	2953 (48.8)	2437 (48.1)		
Missing	60 (1.0)	131 (2.6)		
Collection year				
2003	1,787 (29.5)	1,439 (28.4)		
2004	2,064 (34.1)	1,719 (33.9)	2.47	0.291
2005	2,200 (36.4)	1,907 (37.7)		
Serotypes				
Vaccine	2,129 (35.2)	1,784 (35.2)	3.384	0.066
Non-vaccine	3,209 (53.0)	2,900 (57.3)		
Missing	713 (11.8)	381 (7.5)		
Province				
Gauteng	3,422(56.6)	2,880(56.8)		
Eastern Cape	178(2.9)	292(5.8)		
Western Cape	842(14.0)	588(11.6)		
Mpumalanga	189(3.1)	348(6.9)	891	<0.001
KwaZulu Natal	934(15.4)	282(5.6)		
North West	20 (0.3)	348(6.9)		
Free State	377(6.2)	158(3.1)		
Limpopo	89(1.5)	96(1.9)		
Northern Cape	0(0.0)	73(1.4)		
Specimen Site				
CSF	1,418 (23.4)	1,945 (38.4)		
Blood	4,333 (71.6)	2,866 (56.6)	300	<0.001
Other†	300 (5.0)	254 (5.0)		

Penicillin NonS# No Yes	 3823 (71.6) 1516 (28.4)	 3443 (73.5) 1241 (26.5)	4.52	0.03
Ceftriaxone NonS No Yes	 5294 (99.2) 45 (0.8)	 4646 (99.2) 38 (0.8	0.03	0.86
Rifampicin NonS No Yes	 5072 (95.0) 267 (5.0)	 4520 (96.5) 164 (3.5)	13.64	<0.001
Cotrimoxazole NonS No Yes	 2249 (42.1) 3090 (57.9)	 2252 (48.1) 2432 (51.9)	35.76	<0.001
Erythromycin NonS No Yes	 4624 (86.6) 715 (13.4)	 4057(86.6) 627 (13.4)	0.001	0.99
Clindamycin NonS No Yes	 4809 (90.1) 530 (9.9)	 4209 (89.9) 475 (10.1)	0.13	0.72
Chloramphenicol NonS No Yes	 5192(97.2) 147(2.8)	 4543 (97) 141(3.0)	0.59	0.44
Missing††	713 (11.8)	381 (7.5)		

*Missing values not included in chi squared test
†† Missing data for antibiotic susceptibility testing.
# NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

3.3.2 Comparison of cases from enhanced sites with and without case report forms (Table 3.2).

Of the 6051 cases from enhanced sites 4961(82%) had case report forms and 1090(18%) had no case report forms. Generally there was more missing data in cases without case report forms. The distribution of cases with and without CRFs differed by province (P=<0.001). There was also a significant difference in the type of specimens taken between cases with case report forms and those without case report forms, showing higher proportions in blood culture (23.9%) and CSF (71.8%) among cases with case report forms compared to those without case report forms, blood culture (21.3%) and CSF (70.6%) (P=<0.001). No differences were noted in antibiotic resistance between cases with and without case report forms.

Table 3.2: Demographic and Microbiologic Characteristics of patients with invasive pneumococcal disease from enhanced sites with and without Case Report Forms

	Case Report Forms (n=4961)	No Case Report Forms (n=1090)		
Characteristic	N (%)	N (%)	*X^2	P
Age group in years				
<1	940/ (19.0)	146 (13.4)		
1-4	860 (17.3)	142 (13.0)		
5-14	473 (9.5)	84 (7.7)		
15-24	310 (6.2)	41 (3.8)	7.3	0.292
25-44	1,716(34.6)	319 (29.3)		
45-64	521 (10.5)	100 (9.2)		
=>65	133 (2.7)	19 (1.7)		
Missing	8 (0.2)	239 (21.9)		
Sex				
Male	2516 (50.7)	522 (47.9)	0.038	0.846
Female	2440 (49.2)	513 (47.1)		
Missing	5 (0.1)	55 (5.1)		
Collection Year				
2003	1387 (27.9)	400 (36.7)		
2004	1782 (35.9)	282 (25.9)	50.0	<0.001
2005	1792 (36.1)	408 (37.4)		
Serotypes				
Vaccine	1745(35.2)	384 (35.2)	0.0813	0.766
Non-vaccine	2640 (53.2)	569 (52.2)		
Missing	575 (11.6)	137 (12.6)		
Province**				
Gauteng	2,742 (55.3)	680 (62.4)	328	<0.001
Eastern Cape	167 (3.4)	11(1.0)		
Western Cape	794(16.0)	48 (4.4)		
Mpumalanga	162 (3.3)	27 (2.5)		
KwaZulu Natal	629 (12.7)	30 (28.0)		
North West	13 (0.3)	7 (0.6.)		
Free State	366 (7.4)	11(1.0)		
Limpopo	88 (1.8)	1 (0.1)		
Specimen Site				
CSF	1186 (23.9)	232 (21.3)	29	<0.001
Blood	3563 (71.8)	770 (70.6)		
Other†	212 (4.3)	88 (8.1)		

Penicillin NonS# No Yes	 3139 (71.6) 1247 (28.4)	 684 (71.8) 269 (28.2)	0.016	0.899
Ceftriaxone NonS No Yes	 4354 (99.3) 32 (0.7)	 940 (98.6) 13 (1.4)	3.77	0.052
Rifampicin NonS No Yes	 4171 (95.0) 215 (5.0)	 901 (94.5) 52 (5.5)	0.507	0.477
Cotrimoxazole NonS No Yes	 1831 (41.8) 2555 (58.3)	 418 (43.9) 535 (56.1)	1.44	0.23
Erythromycin NonS No Yes	 3807 (86.8) 579 (13.2)	 817 (85.7) 136 (14.3)	0.772	0.38
Clindamycin NonS No Yes	 3965(90.4) 421(9.6)	 844(88.6) 109(11.4)	2.96	0.085
Chloramphenicol NonS No Yes	 4272(97.4) 114(2.6)	 920 (96.5) 33 (3.5)	2.18	0.140
Missing††	575 (11.6)	137 (12.6)		

*Missing values not included in chi squared test
** Northern Cape not included, as it had no enhanced sites.
†Other specimens include joint fluid, peritoneal fluid and pleural fluid.
†† Missing data for antibiotic susceptibility testing.
# NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

3.4 Description of cases included in analysis of risk factors for mortality

Of 4,961 cases with completed case report forms, 4,890 had complete data on outcome within 30 days of admission. A total of 71 cases were excluded: 38 cases with missing data on outcome; 30 observations died after 30 days and 3 observations had missing date of death.

There were 1154 (24%) cases of *Streptococcus pneumoniae* meningitis and 3736 (76%) cases of other invasive disease. 2958 (80%) of those classified as other invasive disease had bacteraemic pneumonia, 10% had bacteraemia without focus and a further 2% had pneumococcal isolates from other sterile sites (joint or peritoneal fluid).

3.5 Underlying illness

Of the 4890 patients included in the study 1236 had underlying disease, of these, 73 (5.9%) had diabetes mellitus, 40 (3.2%) had coronary artery disease, 28 (2.3%) had valvular heart disease, 259 (21%) had malnutrition, 52 (4.2%) had liver disease, 94 (7.6%) had renal disease, 51 (4.1%) had cancer, 84 (6.8%) had chronic obstructive airways disease, 38 (3.1%) had cerebral vascular accidents and 11 (0.9%) had burns.

3.6 Antibiotics used during admission.

Data for antibiotic use during admission were only available for year 2005, on 94 % (391/418) of the meningitis patients and 94% (1267/1349) of patients with other invasive disease.

3.6 1 Antibiotics used for treating meningitis

Among 391 patients with meningitis, 297 (76%) received a 3rd generation cephalosporin, 1 (0.3%) received a 4th generation cephalosporin, 81 (21%) received penicillin, 5 (1.3%) received a 1st or 2nd generation cephalosporin, and 7 (1.4%) received a combination of other drugs including chloramphenicol and augmentin.

3.6.2 Antibiotics used for treating patients with other invasive disease

Among 1267 patients with other invasive disease, 265 (21%) received a 3rd generation cephalosporin, 1 (0.1) received a 4th generation cephalosporin, 158 (12.5%) received a 1st or 2nd generation cephalosporin, 552 (44%) received penicillin, 225 (18%) received augmentin and 66 (4.4%) received a combination of other drugs including ciprofloxacin, cotrimoxazole, gentamicin and erythromycin.

3.7 Prior antibiotic use:

Among 575 patients who received antibiotics 2 months prior to admission with an episode of invasive pneumococcal disease, 66% received penicillin, 16% received a cephalosporin and the 18% received a combination of other antibiotics, which included ciprofloxacin, erythromycin, gentamicin and cotrimoxazole

3.8 Comparison of characteristics of cases of meningitis versus other invasive disease

3.8.1 Demographic characteristics (Table 3.3).

Age distribution of cases was significantly different between meningitis cases and other IPD (P=<0.001). Of those with meningitis 26% were children <1 year, 12% were children between 1 and 4 years, 13 % were children between 5 and 14 years, 32% were adults between 25 and 44 years and 0.8% were those older than 64 years.

Of those with other invasive disease 17% were children <1 year, 19% were children between 1 and 4 years, 9% were children between 5 and 14 years, 35% were adults between 25 and 44 years, 11% were adults between 45 and 64 years and 3% were those older than 64 years. Therefore meningitis was more common in the younger age groups whereas other invasive disease was more common in older adults.

There was also a significant difference in racial distribution; a higher proportion of black patients presented with meningitis whereas a higher proportion of coloured patients presented with other invasive disease. There was also a significant difference in the distribution of meningitis and other invasive disease by province with more meningitis reported from Eastern Cape (8.2%), Mpumalanga (8.3%) and

Free State (9.3%) and more cases of other invasive disease reported from Gauteng (58%) and Western Cape (17.8%). These differences were statistically significant (P=<0.001).

Table 3.3: Comparison of demographic characteristics of patients with meningitis versus other invasive pneumococcal disease amongst patients' from enhanced sites with case report forms.

	Meningitis	Other invasive disease		
Characteristic	N (%)	N (%)	X^2	P
Age group in years				
<1	296/1152 (25.7)	625/3730 (16.7)		
1-4	138/1152 (11.9)	711/3730 (19.0)	112	<0.001
5-14	144/1152 (12.5)	323/3730 (8.7)		
15-24	94/1152 (8.2)	213/3730 (5.7)		
25-44	370/1152 (32.1)	1323/3730 (35.5)		
45-64	101/1152 (8.8)	413/3730 (11.1)		
=>65	9 /1152 (0.8)	122/3730 (3.3)		
Sex				
Male	589/1153 (51.0)	1892/3732 (50.7)	0.05	0.818
Female	564/1153 (49.0)	1840/3732 (49.3)		
Race				
Black	1094/1152 (95.0)	3404/3718 (91.5)	16	0.001
White	7/1152 (0.6)	48/3718 (1.3)		
Asian	1/1152 (0.1)	18/3718 (0.5)		
Coloured	50/1152 (4.3)	248/3718 (6.7)		
Collection year				
2003	330/1154 (28.6)	1028/3736 (27.5)	0.72	0.69
2004	406/1154 (35.2)	1359/3736 (36.4)		
2005	418/1154 (36.2)	1349/3736 (36.1)		
Province				
Gauteng	539/1154 (46.7)	2167/3736 (58.0)	349	<0.001
Eastern Cape	95/1154 (8.2)	67/3736 (1.8)		
Western Cape	123/1154 (10.7)	664 /3736 (17.8)		
Mpumalanga	96/1154 (8.3)	62/3736 (1.7)		
KwaZulu Natal	141/1154 (12.2)	481/3736 (12.9)		
North West	5/1154 (0.4)	1/3736 (0.0)		
Free State	107/1154 (9.3)	257/3736 (6.9)		
Limpopo	48/1154 (4.2)	37/3736 (0.9)		

3.8.2 Clinical, microbiologic and other characteristics (Tables 3.4 and 3.5)

There were significant differences observed in most clinical factors between meningitis and other invasive disease. The following factors had higher proportions of cases with other invasive disease compared to meningitis: cotrimoxazole prophylaxis (26% versus 18%), HIV-positive cases (88% versus 82%), cases with underlying medical illness (67% versus 44%), cases who received prior antibiotics within 2 months before first positive pneumococcal isolate (19% versus 14%), cases with cotrimoxazole resistant isolates (60% versus 54%) and smokers (4% versus 2%).

Those with meningitis were more likely to have a Pitt bacteraemia score ≥4 (13% versus 7%) and a higher proportion of them took antibiotics 24 hours before first positive blood/CSF culture (10% versus 5%). There was no difference in proportion of nosocomial infection in the two groups.

Table 3.4: Comparison of microbiologic and other characteristics of cases of meningitis versus other invasive pneumococcal disease amongst patients' from enhanced sites with case report forms.

	Meningitis	Other invasive disease		
Characteristic	N (%)	N (%)	X^2	P
Vaccine-serotypes No Yes	 652/1089 (59.9) 437/1089 (40.1)	 1954 (60.4) 1279 (39.6)	0.10	0.74
Nosocomial Infection No Yes	 1131/1156(98.0) 23/1156 (2.0)	 3624/3736 (97.0) 112/3736 (3.0)	3.3	0.06
Smoking No Yes	 1129/1154 (97.8) 25/1154 (2.2)	 3575/3736 (95.7) 161/3736 (4.3)	11	0.001
Alcohol abuse No Yes	 1122/1154 (97.2) 32/1154 (2.8)	 3633/3736 (97.2) 103/3736 (2.8)	0.0008	0.98
Penicillin NonS# No Yes	 789/1090 (72.4) 301/1090 (27.6)	 2302/3233 (71.2) 931/3233 (28.8)	0.56	0.46
Ceftriaxone NonS No Yes	 1084/1090 (99.5) 6/1090 (0.6)	 32025/3233 (0.8) 8/3233 (99.2)	0.57	0.45
Cotrimoxazole NonS No Yes	 505/1090 (46.3) 585/1090 (53.7)	 1296/3233 (40.0) 1937/3233 (60.0)	13	<0.001
Erythromycin NonS No Yes	 954/1090 (87.5) 136/1090 (12.5)	 2798/3233 (86.6) 435/3233 (13.5)	0.68	0.41
Chloramphenicol NonS No Yes	 1058/1090 (97.1) 32/1090 (2.9)	 3152 (97.5) 81 (2.5)	0.59	0.44

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

Table 3.5: Comparison of clinical characteristics of cases of meningitis versus other invasive pneumococcal disease amongst patients' from enhanced sites with case report forms

	Meningitis	Other invasive disease		
Characteristic	N (%)	N (%)	X^2	P
Cotrimoxazole prophylaxis No Yes	 651/796 (81.8) 145/796 (18.2)	 1922/2618 (73.4) 696/2618 (26.6)	23	<0.001
HIV infection No Yes	 112/624 (18.0) 512/624 (82.0)	 284/2346 (12.1) 2062/2346 (87.9)	14.6	<0.001
Pitt bacteraemia score <4 ≥4	 708/814 (87.0) 106/814 (13.0)	 2467/2657 (92.8) 190/2657 (7.2)	27.7	<0.001
Underlying illness No Yes	 323/578 (55.9) 255/578 (44.1)	 777/2349 (33.1) 1572/2349 (66.9)	102.8	<0.001
Antibiotic treatment past 24 hours No Yes	 884/977 (90.5) 93//977 (9.5)	 2991/3135 (95.4) 144/3135 (4.6)	33	<0.001
Antibiotic treatment past 2 months No Yes	 667/775 (86.1) 108/775 (13.9)	 2004/2471 (81.1) 467/2471 (18.9)	9.97	0.002

3.9 Comparison of characteristics of patients who received and those who did not receive antibiotics within 2 months prior to positive blood/CSF culture (Table 3. 6)

There were significant differences observed in age distribution between the two groups (P=<0.001). Of those who received antibiotics 65% were children < 5 years and 35% were those aged between 5 and 65 years. Among patients aged 25-44 years, 13% received antibiotics compared to 36% in the same age group who did not receive antibiotics.

There was also a significant difference in provincial distribution with a higher proportion of patients who received antibiotics reported from Western Cape and Gauteng Provinces (39.8% and 38.4%) respectively. These observed differences were statistically significant (P=<0.001). Other significant differences were observed in distribution of vaccine-serotypes (61.4% versus 35.7%, P=<0.001), cotrimoxazole prophylaxis (64.9% versus 14.4%, P=<0.001), HIV infection (93.4% versus 83.2%, P<0.001) and underlying illness (81.9% versus 61.5% P=<0.001). Patients who received antibiotics had higher proportions of antibiotic resistant isolates e.g. penicillin (46.2% versus 25.9%, P=<0.001). No differences however were observed in severity of illness (P=0.49).

Table 3.6: Comparison of characteristics of patients who received and those who did not receive antibiotics 2 months prior to positive blood/CSF culture

	Received antibiotics	Did not receive antibiotics		
Characteristic	N (%)	N (%)	X^2	P value
Age group in years				
<1	180/575 (31.3)	524/2668 (19.6)	249	<0.001
1-4	197/575 (34.3)	408/2668 (15.3)		
5-14	81/575 (14.1)	255/2668 (9.6)		
15-24	13/575 (2.3)	173/2668 (6.5)		
25-44	75/575 (13.0)	979/2668 (36.7)		
45-64	23/575 (4.0)	261/2668 (9.7)		
≥65	6/575 (1.0)	68/2668 (2.6)		
Sex				
Male	289/575 (50.3)	1338/2667 (50.2)	0.002	0.97
Female	286/575 (49.7)	1329/2667 (49.8)		
Province				
Gauteng	221/575 (38.4)	1488/2671 (55.7)	319	<0.001
Eastern Cape	28/575 (4.9)	117/2671 (4.4)		
Western Cape	229/575 (39.8)	280/2671 (10.5)		
Mpumalanga	10/575 (1.7)	123/2671 (4.6)		
KwaZulu Natal	29/575 (5.0)	292/2671 10.9)		
North West	1/575 (0.2)	3/2671 (0.1)		
Free State	45/575 (7.9)	314/2671 (11.8)		
Limpopo	12 /575(2.1	54/2671 (2.0)		
Serotypes				
Non-vaccine	201/520 (38.6)	1529/2379 (64.3)	116	<0.001
Vaccine	319/520 (61.4)	850/2379 (35.7)		
Cotrimoxazole prophylaxis				
No	183/522 (35.1)	2168/2532 (85.6)	624	<0.001
Yes	339/522 (64.9)	364/2532 (14.4)		
HIV infection				
No	28/424 (6.6)	289/1722 (16.8)	28	<0.001
Yes	396 /424 (93.4)	1433/1722 (83.2)		
Underlying illness				
No	66/365 (18.1)	608/1577 (38.5)	54.8	<0.001
Yes	299/365 (81.9)	969/1577 (61.5)		
Pitt bacteraemia score				
<4	325/353 (92.0)	1710/1837 (93.1)	0.47	0.49
≥4	28/353 (7.9)	127/1837 (6.9)		

Cd4 count Low Normal	 104/159 (65.4) 55/159 (34.6)	 155 /546 (28.4) 391/546 (71.6)	2.2	0.13
Penicillin NonS# No Yes	 280/520 (53.9) 240/520 (46.2)	 1763/2380 (74.1) 617/2380 (25.9)	83.9	<0.000
Ceftriaxone NS No Yes	 507/520 (97.5) 13/520 (2.5)	 2373/2380 (99.7) 7/2380 (0.3)	30	<0.001
Cotrimoxazole NS No Yes	 94/520 (18.1) 426 /520 (81.9)	 1102/2380 (46.3) 1278/2380 (53.7)	140	<0.001
Erythromycin NS No Yes	 380/520 (73.1) 140/520 (26.9)	 2127/2380 (89.4) 253/2380 (10.6)	96.7	<0.001
Chloramphenicol NS No Yes	 508/520 (97.6) 12/520 (2.3)	 2321/2380 (97.5) 59/2380 (2.5)	0.05	0.82

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

3.10 Comparison of characteristics of HIV-positive and HIV-negative patients with invasive pneumococcal disease (Table 3.7)

Data for HIV was available for 2970 (61%) of our study sample; of this 2577 (87%) were HIV co-infected. Age distribution between the two groups was significantly different (P=<0.001). Of those who had HIV co-infection, 34% were children <5 years and 41% were adults aged 25-44 years while those who did not have HIV co-infection 56% were children <5 years and 15% were adults aged 25-44 years.

There was higher proportion of HIV-infected patients reported from Gauteng (64.6%) and Western Cape (11.7%) provinces compared to (55%) from Gauteng and (19.6%) from Western Cape in the HIV-negative patients. This observed difference was statistically significant (P=<0.001). Other significant differences were observed in distribution of vaccine-serotypes (42.4% versus 34.3%, P <0.001), cotrimoxazole prophylaxis (38.7% versus 8.0%, P=<0.001) and underlying illness (65.4% versus 55.1%, P=<0.001). There was a higher proportion of female patients with HIV infection (52% versus 41%) and also a higher proportion of antibiotic resistant isolates among the HIV co-infected patients e.g. penicillin (32.0% versus 25.0%, P=<0.001). There were no differences observed in severity of illness between HIV-positive and HIV-negative patients (P=0.14).

Table 3.7: Comparison of characteristics of HIV-positive and HIV-negative patients with invasive pneumococcal disease

	HIV-positive	HIV-negative		
Characteristic	N (%)	N (%)	X^2	P value
Age group in years				
<1	393/2574 (15.3)	131/393 (33.3)		
1-4	488/2574 (19.0)	92 /393 (23.4)		
5-14	235 /2574 (9.1)	45/393 (11.5)	149	<0.001
15-24	145/2574 (5.6)	20/393 (5.1)		
25-44	1061/2574 (41.2)	60 /393 (15.3)		
45-64	235/2574 (9.1)	33/393 (8.4)		
≥65	17/2574 (0.7)	12/393 (3.0)		
Sex				
Male	1235/2574 (48.0)	230/392 (59.0)	15	<0.001
Female	1339/2574 (52.0)	162/392 (41.0)		
Province				
Gauteng	1664/2577 (64.6)	216/393 (55.0)		
Eastern Cape	95 /2577 (3.7)	29/393 (7.4)		
Western Cape	301/2577 (11.7)	77/393 (19.6)	47	<0.001
Mpumalanga	56/2577 (2.2)	4/393 (1.0)		
KwaZulu Natal	230/2577 (8.9)	19/393 (4.8)		
North West	4/2577 (0.2)	0/393 (0.0)		
Free State	205/2577 (7.9)	43/393 (10.9)		
Limpopo	22/2577 (0.8)	5/393 (1.3)		
Serotypes				
Vaccine	956/2253 (42.4)	121/353 (34.3)	8.4	0.004
Non-vaccine	1297/2253 (57.6)	232/353 (65.7)		
Cotrimoxazole prophylaxis				
Yes	737/1906 (38.7)	26/322 (8.0)	114	<0.001
No	1169/1906 (61.3)	296/322 (92.0)		
Underlying illness				
Yes	1107/1693 (65.4)	129/234 (55.1)	9.4	0.002
No	586/1693 (34.6)	105/234 (44.9)		
Pitt bacteraemia score				
<4	1683/1823 (92.3)	256 /285 (89.8)	2.0	0.149
≥4	140 /1823 (7.7)	29/285 (10.2)		

Penicillin NonS# No Yes	 1532/2254 (68.0) 722/2254 (32.0)	 265/353 (75.0) 88/353 (25.0)	7.0	0.007
Ceftriaxone NonS No Yes	 2237/2254 (99.2) 17/2254 (0.8)	 350/353 (99.1) 3/353 (0.9)	0.03	0.85
Cotrimoxazole NonS No Yes	 812/2254 (36.0) 1442/2254 (64.0)	 166/353 (47.0) 187/353 (53.0)	15.8	<0.001
Erythromycin NonS No Yes	 1907/2254 (84.6) 347/2254 (15.4)	 319/353 (90.4) 34/353 (9.6)	8.1	0.004
Chloramphenicol NonS No Yes	 2183/2254 (96.9) 71/2254 (3.1)	 345/353 (97.7) 8/353 (2.3)	0.81	0.37

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics

3.11 Outcome

The overall case fatality rate was 1360/4890 (27.8%) of which 911 (67%) patients died within 2 days of admission and 449 (33%) died between 2 days and 30 days of admission. The median age of those who died was 30 years (range 0 to 86 years). The median duration of outcome from a positive blood/CSF culture was 6 hospital days**.** Meningitis had a higher case fatality rate 520/1154 (45.1%) compared to other invasive disease 840/3736 (22.5%).

3.12 Risk factors associated with mortality in all eligible patients with IPD

3.12.1 Univariate analysis (Tables 3.8.1 –3.8.4).

The following factors were found to be significantly associated with mortality on univariate analysis using Pearsons X^2 test at $P \leq 0.1$.

- Demographic factors: age, sex, race and province.
- Microbiologic factors: specimen type and cotrimoxazole resistance.
- Clinical factors: Pitt bacteraemia score, prior antibiotic use 24 hours before first positive blood/CSF culture, prior antibiotic use within 2 months before first positive blood/CSF culture and HIV status.

Table 3.8.1: Univariate analysis of demographic factors that could potentially influence mortality in patients with invasive pneumococcal disease.

Risk Factor	Case Fatality Rate (%)	X^2	P value
Age group in years			
<1	277/921 (30.1)	159.68	<0.001
1-4	151/849 (17.8)		
5-14	77/467 (16.5)		
15-24	72/307 (23.4)		
25-44	498/1693 (29.4)		
45-64	225/514 (43.8)		
=>65	56/131 (42.8)		
Sex			
Male	665/2481 (26.8)	2.7	0.10
Female	695/2404 (28.9)		
Race			
Black	1270/4498 (28.2)		
White	15/55 (27.3)	7.8	0.05
Asian	6/19 (31.6)		
Coloured	62/298 (20.8)		
Collection year			
2003	385/1358 (28.4)	1.68	0.43
2004	503/1765 (28.5)		
2005	472/1767 (26.7)		
Province			
Gauteng	787/2706 (29.1)	86.58	<0.001
Eastern Cape	67/162 (41.4)		
Western Cape	136/787 (17.3)		
Mpumalanga	64/158 (40.5)		
KwaZulu Natal	170/622 (27.3)		
North West	5/6 (83.3)		
Free State	99/364 (27.2)		
Limpopo	32/85 (37.7)		

Case Fatality Rate: Number of deaths /Number of patients (%).Number of deaths included only those who died within 30 days of admission

Table 3.8.2: Univariate analysis of microbiologic and other factors that could potentially influence mortality in patients with invasive pneumococcal disease

Risk Factor	Case Fatality Rate[f](%)	X^2	P value
Vaccine-serotypes No Yes	 735/2606 (28.2) 472/1716 (27.5)	0.25	0.617
Specimen site Other† CSF	 840/3737 (22.5) 520 /1154 (45.0)	224	<0.001
Nosocomial infection No Yes	 1323/4755 (27.8) 37/135 (27.4)	0.01	0.92
Alcohol use No Yes	 1321/4755 (27.8) 39/135 (28.9)	0.08	0.77
Current smoker No Yes	 1318/4704 (28.0) 42/186 (22.6)	2.64	0.10

†Other specimens include blood, joint fluid, peritoneal fluid and pleural fluid.

[f] Case Fatality Rate: Number of deaths /Number of patients (%). Number of deaths included only those who died within 30 days of admission

Table 3.8.3: Univariate analysis of the potential influence of antibiotic resistance on mortality in patients with invasive pneumococcal disease

Risk Factor	Case Fatality Rate (%)	X^2	P
Penicillin NonS#			
No	868/3091 (28.1)	0.10	0.75
Yes	340/1232 (27.6)		
Ceftriaxone NonS			
No	1201/4292 (28.0)	0.44	0.50
Yes	7/31 (22.6)		
Rifampicin NonS			
No	1158/4115 (28.0)	1.66	0.198
Yes	50/208 (24.0)		
Cotrimoxazole NonS			
No	532/1801 (29.5)	3.9	0.05
Yes	676/2522 (26.8)		
Erythromycin NonS			
No	1040/3752 (27.7)	0.71	0.398
Yes	168/571 (29.4)		
Clindamycin NonS			
No	1082/3907 (27.7)	1.26	0.26
Yes	126/416 (30.3)		
Chloramphenicol NonS			
No	32/113 (28.3)	0.008	0.93
Yes	1176/4210 (27.9)		
Tetracycline NonS			
No	989/3569 (27.7)	0.55	0.46
Yes	219/745 (29.0)		

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

[f] Case Fatality Rate: Number. of deaths /Number. of patients (%).Number of deaths included only those who died within 30 days of admission

Table 3.8.4: Univariate analysis of clinical factors that could potentially influence mortality in patients with invasive pneumococcal disease

Risk Factor	Case Fatality Rate (%)	X^2	P
Pitt bacteraemia score <4 ≥4	 765/3175 (24.1) 195/296 (65.9)	236.3	<0.001
HIV infection No Yes	 69/396 (17.4) 655/2574 (25.5)	11.98	0.001
Cotrimoxazole prophylaxis No Yes	 534/2573 (20.8) 170/841 (20.2)	0.11	0.74
Prior antibiotic use (24 hours) No Yes	 979/3875 (25.3) 72/237 (30.4)	3.07	0.08
Prior antibiotic use (2 months) No Yes	 547/2671 (20.5) 138/575 (24.0)	3.5	0.06

[f] Case Fatality Rate: No. of deaths /No. of patients (%). Number of deaths included only those who died within 30 days of admission.

3.12.2 Multivariate analysis (Table 3.9)

There were no interactions observed. The following factors were significantly associated with mortality in multivariate analysis adjusting for the effects of each in the model.

3.12.2.1 Demographic factors:

- Age: Compared to patients less than 1 year of age those aged 1-4 years (OR 0.47, CI 0.29 – 0.75, P=0.002), 5-14 years (OR 0.37, CI 0.20 – 0.66, P=0.001) 15-24 years (OR 0.28, CI 0.12 – 0.64, P=0.003) and 25-44 years (OR 0.56, CI 0.37 – 0.83, P=0.005) were less likely to die. Patients aged 15-24 years had lowest likelihood of dying while patients aged 45-64 (OR 1.13, CI 0.66 – 1.94, P=0.65) and ≥65 (OR 1.0, CI 0.24 – 4.21 P=0.99) were not at significantly different risk of dying as compared to those <1 year old.

- Province: Compared to patients from Gauteng, patients from Mpumalanga (OR 2.0 CI 0.96 – 4.1, P= 0.058), Eastern Cape (OR 1.6, CI 0.91 – 2.8, P=0.101) and KwaZulu Natal (OR 1.4, CI 0.80 – 2.4, P=0.24) were more likely to die. However, this was not a statistically significant association. Patients from Western Cape were significantly less likely to die (OR 0.27, CI 0.15 – 0.50, P=<0.001) compared to other provinces.

3.12.2.2 Microbiologic factors:

- Meningitis: Patients with meningitis were 2.8 times more likely to die compared to those with other invasive pneumococcal disease i.e. bacteraemia (OR 2.8, CI 1.9 – 3.9, P=<0.001)

3.12.2.3 Clinical factors:

- HIV Infection: HIV-positive invasive pneumococcal disease patients had almost 3 times the risk of dying compared to HIV-negative invasive pneumococcal disease patients (OR 2.8, CI 1.6 – 4.6, P=<0.001).
- Pitt bacteraemia score: Patients admitted with severe state of illness (Pitt bacteraemia score ≥4) were nearly 5 times at risk of dying (OR 4.7, CI 2.8 – 7.7, P=<0.001).
- Prior antibiotic use within 2 months before first positive culture: Patients who took an antibiotic other than cotrimoxazole prophylaxis within two months prior to admission with an episode of invasive disease had two times the risk of dying from the episode compared to patients who did not take an antibiotic (OR 2.1, CI 1.4 – 3.1, P=<0.001).

Table 3.9: Multivariate analysis of factors potentially associated with mortality in all invasive pneumococcal disease

Risk Factor	Odds Ratio (Adjusted)	95% CI	P
Age group in years			
<1	1.0	Reference	-
1-4	0.47	0.29 – 0.75	0.002
5-14	0.37	0.20 – 0.66	0.001
15-24	0.28	0.12 – 0.64	0.003
25-44	0.56	0.37 – 0.83	0.005
45-64	1.13	0.66 – 1.94	0.65
=>65	1.0	0.24 – 4.21	0.99
Province			
Gauteng	1.0	Reference	-
Eastern Cape	1.6	0.91 – 2.8	0.101
Western Cape	0.27	0.15 – 0.50	<0.001
Mpumalanga	2.0	0.96 – 4.1	0.058
KwaZulu Natal	1.4	0.80 – 2.4	0.24
North West	N/A	-	-
Free State	0.91	0.60 – 1.4	0.68
Limpopo	0.36	0.08 – 1.7	0.20
Clinical syndrome			
Other IPD	1.0	Reference	-
Meningitis	2.8	1.9 – 3.9	<0.001
HIV infection			
No	1.0	Reference	-
Yes	2.8	1.6 – 4.6	<0.001
Pitt bacteraemia score			
<4	1.0	Reference	-
≥4	4.7	2.8 – 7.7	<0.001
Prior antibiotic use (2months)			
N o	1.0	Reference	-
Yes	2.1	1.4 – 3.1	<0.001

We considered that risk factors for death might differ between patients with meningitis as compared to other IPD as meningitis is associated with a higher mortality overall. Pharmacodynamic factors and management may also be very different between these groups.

3.13 Risk factors for death in patients with meningitis (Table 3.10).

3.13.1 Univariate analysis

The following factors were significant risk factors for death on univariate analysis in the meningitis group and were included in the multivariable logistic regression model.

- Demographic factors: age, race and province.
- Microbiologic factors: vaccine- serotypes and penicillin resistance.
- Clinical factors: HIV status, Pitt bacteraemia, prior antibiotic use within 2 months before first positive blood /CSF culture

3.13.2 Multivariate analysis

Factors significantly associated with mortality in multivariate analysis.

3.13.2.1 Demographic factors:

- Age: Children less than 1 year of age and adults ≥45 years with pneumococcal meningitis were more likely to die compared to other age groups.
- Province: Patients living in Eastern Cape had 2.3 times the risk of dying (OR 2.3, CI 1.4 – 3.9, P=0.002) while those from Mpumalanga had 3.1 times the risk of dying (OR 3.1, CI 1.6 – 6.2, P=0.001) if they had an episode of pneumococcal meningitis. Patients from Western Cape had 0.26 times the risk of dying (OR 0.26, CI 0.15 – 0.48, P=<0.001).

3.13.2.2 Clinical factors:

- HIV Infection: HIV-positive pneumococcal meningitis patients had nearly twice the risk of dying compared to HIV-negative meningitis patients (OR 2.2, CI 1.3 – 3.6, P=0.002).
- Pitt bacteraemia score: Pneumococcal meningitis patients admitted to hospital with Pitt bacteraemia score ≥4 had 5 times the risk of dying (OR 5.0, CI 3.1 – 8.1, P=<0.001).
- Prior antibiotic use within 2 months before first positive blood/CSF culture: The risk of dying in pneumococcal meningitis patients with a history of prior antibiotics use 2 months before admission was twice those in patients without prior antibiotic use (OR 2.0, CI 1.4 – 3.0, P=<0.001).

Table 3.10: Univariate and multivariate analysis of risk factors influencing mortality in patients with pneumococcal meningitis

	Univariate analysis			Multivariate analysis	
Risk Factor	Case Fatality Rate (%)	OR (95% CI) Unadjusted	P	OR (95% CI) Adjusted	P
Age group					
<1	117/296(39.5)	1.0	Reference	1.0	Reference
1-4	43/138 (31.2)	0.69 (0.5, 1.1)	0.09	0.42 (0.27,0.67)	<0.001
5-14	45/144 (31.2)	0.69 (0.5, 1.1)	0.09	0.42 (0.23,0.74)	0.003
15-24	35/94 (37.2)	0.90 (0.6, 1.5)	0.69	0.27 (0.12,0.61)	0.002
25-44	205/370(55.4)	1.9 (1.4, 2.6)	<0.001	0.52 (0.35,0.77)	0.001
45-64	70/101(69.3)	3.5 (2.1, 5.6)	<0.001	1.1 (0.63, 1.8)	0.80
≥65	4 /9 (44.4)	1.2 (0.3, 4.7)	0.77	0.71 (0.17,2.9)	0.64
Sex					
Male	258/589(43.8)	1.0	Reference		
Female	262/564(46.6)	1.1 (0.9, 1.4)	0.37	NI*	-
Race					
Black	508/1094(46.4)	1.0	Reference		
White	2/7 (28.6)	0.46 (0.1, 2.4)	0.36	NS**	-
Asian	1/1 (100)	NA	-		
Coloured	9/50(18.0)	0.25 (0.1, 0.5)	<0.001		
Collection year					
2003	146/330(44.2)	1.0	Reference		
2004	193/406 (47.5)	1.1 (0.9, 1.5)	0.37	NI	-
2005	181/418 (43.3)	0.96 (0.7,1.3)	0.79		
Serotypes					
Non-vaccine	323/652 (49.5)	1.0	Reference		
Vaccine	171/437 (39.1)	0.65 (0.5, 0.8)	0.001	NS	-
Province					
Gauteng	263/539 (48.8)	1.0	Reference	1.0	-
Eastern Cape	49/95 (51.6)	1.1 (0.7, 1.7)	0.62	2.3 (1.4, 3.9)	0.002
Western Cape	26/123 (21.1)	0.28 (0.2, 0.4)	<0.001	0.26 (0.15,0.48)	<0.001
Mpumalanga	45/96 (46.9)	0.93 (0.6, 1.4)	0.73	3.1 (1.6, 6.2)	0.001
KwaZulu Natal	64/141 (45.4)	0.87 (0.6, 1.2)	0.47	1.5 (0.88,2.5)	0.14
North West	5/5 (100.0)	N/A		N/A	
Free State	44/107 (41.0)	0.73 (0.5, 1.1)	0.15	1.0 (0.66, 1.5)	0.97
Limpopo	24/48 (50.0)	1.0 (0.6, 1.9)	0.87	0.44 (0.09,2.0)	0.29

Nosocomial infection No Yes	 510 (45.1) 10 (43.5)	 1.0 0.93 (0.4,2.2)	 Reference 0.88	 NI*	 -
Current smoker No Yes	 510 (45.2) 10 (40.0)	 1.0 0.8 1(0.4, 1.8)	 Reference 0.60	 NI	 -
HIV infection No Yes	 21/112 (18.8) 241/512(47.0)	 1.0 3.9 (2.3, 6.4)	 Reference <0.001	 2.2 (1.3,3.6)	 0.002
Alcohol use No Yes	 503/1122(44.8) 17/32 (53.1)	 1.0 1.4 (0.7, 2.8)	 Reference 0.35	 NI	 -
Underlying illnesses No Yes	 137/323 (42.4) 120/255 (47.1)	 1.0 1.2 (0.9, 1.7)	 Reference 0.27	 NI	 -
Pitt bacteraemia score <4 ≥4	 288/708 (40.7) 81/106 (76.4)	 1.0 4.7 (2.9, 7.6)	 Reference <0.001	 5.0 (3.1,8.1)	 <0.001
Prior antibiotic use (24 hours) No Yes	 377/884 (42.7) 36/93 (38.7)	 1.0 0.84 (0.5, 1.3)	 Reference 0.47	 NI	 -
Prior antibiotic use (2 months) No Yes	 244/667 (36.6) 41/108 (38.0)	 1.0 1.1 (0.7, 1.6)	 Reference 0.78	 2.0 (1.4,3.0)	 <0.001
Cotrimoxazole prophylaxis No Yes	 228/651 (35.0) 59/145 (40.7)	 1.0 1.3 (0.9, 1.8)	 Reference 0.20	 NI	 -
Penicillin NonS# No Yes	 374/789 (47.4) 121/301 (40.2)	 1.0 0.75 (0.6, 0.9)	 Reference 0.03	 NS	 -
Ceftriaxone NonS No Yes	 493/1084(45.5) 2/6 (33.3)	 1.0 0.60 (0.1, 3.3)	 Reference 0.56	 NI	 -
Chloramphenicol Non No Yes	 479/1058(45.3) 16 /32(50.0)	 1.0 1.2 (0.6, 2.4)	 Reference 0.60	 NI	 -

*NI: Factors not significant on univariate analysis (P>0.10) were omitted in logistic regression model.

**NS: Factors not significant on multivariate logistic regression analysis

[f] Number of deaths included only those who died within 30 days of admission.

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

3.14 Risk factors for death in patients with other invasive pneumococcal disease (Table 3.11)

3.14.1 Univariate analysis

The following risk factors significant on univariate analysis stratified for other invasive disease were included in the multivariable logistic regression model:

- Demographic factors: age, and province.
- Microbiologic factors: vaccine-serotypes and erythromycin resistance.
- Clinical factors: HIV status, Pitt bacteraemia score, prior antibiotic use within 2 months before first positive blood/CSF culture.

3.14.2 Multivariate analysis

Risk factors significantly associated with mortality in patients with other invasive pneumococcal disease in multivariate analysis were:

3.14.2.1 Demographic factors:

- Age: Children less than 1 year of age and adults ≥45 years of age with other invasive pneumococcal disease were more likely to die compared to other age groups.
- Province: Patients who lived in Eastern Cape had 2.7 times the risk of dying (OR 2.7, CI 1.7 – 4.2, P=<0.001) while those from Mpumalanga had. 3.3 times the risk of dying (OR 3.3, CI 2.1 – 5.2, P=<0.001) if they had other invasive pneumococcal disease. Patients from Western Cape showed a less likelihood of dying (OR 0.48, CI 0.33 – 0.70, P=<0.001).

3.14.2.2 Clinical factors:

- Pitt bacteraemia score: Patients with Pitt bacteraemia of ≥4 with a positive blood culture for pneumococci had 5.5 times the risk of dying (OR 5.5, CI 3.8 – 7.9, P=<0.001).
- Patients with history of prior antibiotic use within 2 months before first positive blood/CSF culture had 1.8 times the risk of dying (OR 1.8, CI 1.3 – 2.4, P=<0.001).

Table 3.11 Univariate and multivariate analysis of risk factors influencing mortality in patients with other invasive disease

	Univariate analysis			Multivariate analysis	
Risk Factor	Case Fatality Rate (%)	OR (95% CI) Unadjusted	P	OR (95% CI) Adjusted	P
Age group					
<1	160/625 (25.6)	1.0	Reference	1.0	Reference
1-4	108/711 (15.2)	0.52 (0.39,0.68)	<0.001	0.41 (0.28,0.60)	<0.001
5-14	32/323 (9.9)	0.32 (0.21,0.48)	<0.001	0.39 (0.25,0.61)	<0.001
15-24	37/213 (17.4)	0.61 (0.41,0.90)	0.015	0.24 (0.12,0.48)	<0.001
25-44	293/1323(22.2)	0.83 (0.66, 1.0)	0.09	0.57 (0.42,0.77)	<0.001
45-64	155/413 (37.5)	1.7 (1.3, 2.3)	<0.001	1.3 (0.88, 1.9)	0.18
≥65	52/122 (42.6)	2.2 (1.4, 3.2)	<0.001	1.5 (0.76,2.8)	0.25
Sex					
Male	407/1892(21.5)	1.0	Reference		
Female	433/1840(23.5)	1.1 (0.96,1.3)	0.14	NI*	-
Race					
Black	762/3404(22.4)	1.0	Reference		
White	13/48 (27.1)	1.3 (0.68, 2.4)	0.44	NI	-
Asian	5/18 (27.8)	1.3 (4.7, 3.8)	0.59		
Coloured	53/248 (21.4)	0.94 (0.69, 1.3)	0.71		
Collection year					
2003	239/1028(23.3)	1.0	Reference		
2004	310/1359(22.8)	0.98 (0.80, 1.2)	0.80	NI	-
2005	291/1349(21.6)	0.91 (0.75, 1.1)	0.33		
Serotypes					
Non-vaccine	412/1954(21.1)	1.0	Reference	NS**	-
Vaccine	301/1279(23.5)	1.2 (0.98, 1.4)	0.10		
Province					
Gauteng	524/2167(24.2)	1.0	Reference	1.0	-
Eastern Cape	18/67 (26.9)	1.2 (0.67, 2.0)	0.61	2.7 (1.7,4.2)	<0.001
Western Cape	110/664 (16.6)	0.62(0.49,0.78)	<0.001	0.48 (0.33,0.70)	<0.001
Mpumalanga	19/62 (31.0)	1.4 (0.80, 2.4)	0.24	3.3 (2.1,5.2)	<0.001
KwaZulu Natal	106/481 (22.0)	0.89 (0.70, 1.1)	0.32	0.92 (0.62, 1.4)	0.66
North West	0 (0.0)	N/A	-	N/A	-
Free State	55/257 (21.4)	0.85 (0.62, 1.2)	0.32	1.2 (0.81,1.6)	0.42
Limpopo	8 /37 (21.6)	0.86 (0.39, 1.9)	0.72	2.0 (1.1, 3.9)	0.030

Nosocomial infection No Yes	 813/3624(22.4) 27/112 (24.1)	 1.0 1.1 (0.71, 1.7)	 Reference 0.68	 NS	 -
Current smoker No Yes	 808/3575(22.6) 32/112 (20.0)	 1.0 0.85(0.57,1.3)	 Reference 0.42	 NI	 -
HIV infection No Yes	 48/284 (16.9) 414/2062(20.1)	 1.0 1.2 (0.89, 1.7)	 Reference 0.21	 NI	 -
Alcohol use No Yes	 818/3633(22.5) 22/103 (21.4)	 1.0 0.93(0.58,1.5)	 Reference 0.78	 NI	 -
Underlying illnesses No Yes	 154/777(19.8) 373/1572(23.7)	 1.0 1.3 (1.02, 1.6)	 Reference 0.03	 NS	 -
Pitt bacteraemia score <4 ≥4	 452/2326(19.4) 113/185 (61.1)	 1.0 6.3 (4.6, 8.5)	 Reference <0.001	 5.5(3.8,7.9)	 <0.001
Prior antibiotic use (24h) No Yes	 602/2991(20.0) 36/144 (25.0)	 1.0 1.3 (0.90, 1.9)	 Reference 0.16	 NI	 -
Prior antibiotic use (2m) No Yes	 303/2004(15.0) 97/467 (20.8)	 1.0 1.5 (1.1,1.9)	 Reference 0.003	 1.8(1.3,2.4)	 <0.001
Cotrimoxazoleprophylaxis No Yes	 306/1922(15.9) 111/696 (16.0)	 1.0 (0.79, 1.3)	 Reference 0.99	 NI	 -
Penicillin NonS# No Yes	 494/2302(21.5) 219/931 (23.5)	 1.0 1.1 (0.93, 1.3)	 Reference 2.0	 NI	 -
Ceftriaxone NonS No Yes	 708/3208(22.1) 5/25 (20.0)	 1.0 0.88(0.33,2.4)	 Reference 0.80	 NI	 -
Cotrimoxazole NonS No Yes	 277/1296(21.4) 436/1937(22.5)	 1.0 1.1 (0.90, 1.3)	 Reference 0.44	 NI	 -
Erythromycin NonS No Yes	 600/2798(21.4) 113/435 (26.0)	 1.0 1.3 (1.02, 1.6)	 Reference 0.03	 NS	 -

NI*: Factors not significant on univariate analysis (P>0.10) were omitted in logistic regression model.

NS**: Factors not significant on multivariate logistic regression analysis

[f] Number of deaths included only those who died within 30 days of admission

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned antibiotics.

Analysis of risk factors in meningitis and other invasive pneumococcal disease showed that risk factors for death in both groups were similar except for HIV infection which was a risk factor in meningitis patients but not in patients with other IPD as shown in Tables 3.10 and 3.11**.**

3.15 Low CD4+ count as a risk factor for death in all IPD patients with HIV co-infection (Table 3.12)

3.15.1 Univariate analysis

The following factors were significant risk factors for death on univariate analysis and were included in the multivariable logistic regression model:

- Demographic factors: age and province.
- Microbiologic factors: erythromycin resistance.
- Clinical factors: Low CD4+ count, Pitt bacteraemia score, prior antibiotic use within 2 months before first positive blood /CSF culture, prior antibiotic use 24 hours before first positive blood /CSF culture.

3.15.2 Multivariate analysis

Factors significantly associated with mortality in multivariate analysis.

3.15.2.1 Demographic factors:

- Age: Children less than 1 year of age and adults ≥45 years with HIV infection were more likely to die compared to other age groups even though there was no statistically significant difference.

3.15.2.2 Clinical factors:

- Pitt bacteraemia score: HIV co-infected patients who were admitted to hospital with Pitt bacteraemia score ≥4 had 3.4 times the risk of dying (OR 3.4, CI 1.5 – 7.9, P=0.004.
- Meningitis: Meningitis patients with HIV co-infection had 4.5 times the risk of dying compared to those with other invasive pneumococcal disease (OR 4.5, CI 2.4 – 8.5, P=<0.001).

- CD4+ count: Patients were 3.7 times more likely to die if their CD4+ count was low (OR 3.7, CI 1.5 – 8.7, P=<0.004).
- Prior antibiotic use within 2 months before first positive blood /CSF culture (OR 1.9, CI 0.92 – 3.9, P=0.085) and erythromycin (OR 1.4, CI 0.62 – 2.9, P=0.44) were not significantly associated with death.

Table 3.12: Univariate and multivariate analysis to assess CD4+ count as a risk factor for mortality in HIV-positive patients with invasive pneumococcal disease

	Univariate analysis			Multivariate analysis	
Risk Factor	Case Fatality Rate (%)	OR (95% CI) Unadjusted	P	OR (95% CI) Adjusted	P
Age group					
<1	124/393 (31.6)	1.0	Reference	1.0	Reference
1-4	84 /488 (17.2)	0.45(0.33, 0.62)	<0.001	0.34(0.11,1.0)	0.053
5-14	40/235 (17.0)	0.44(0.30, 0.66)	<0.001	0.71(0.19,2.6)	0.60
15-24	34/145 (23.5)	0.66(0.43,1.03)	0.068	0.17(0.02,1.5)	0.11
25-44	285/1061(26.9)	0.79(0.62,1.03)	0.078	0.87(0.36,2.1)	0.76
45-64	83/235 (35.3)	1.290.84, 1.7)	0.33	1.3(0.39,3.9)	0.70
≥65	6/17 (35.3)	1.2(0.43, 3.3)	0.75	3.2(0.28,38.4)	0.35
Sex					
Male	307/1235 (24.9)	1.0	Reference	NI*	-
Female	350/1339 (26.1)	1.1(0.89, 1.3)	0.46		
Serotypes					
Non-vaccine	334/1297 (25.8)	1.0	Reference	NI*	-
Vaccine	245/956 (25.6)	0.99(0.82,1.2)	0.95		
Specimen site					
Other IPD	416/2065 (20.2)	1.0	Reference	1.0	Reference
CSF	241/512 (47.0)	3.5 (2.9, 4.3)	<0.001	4.5 (2.4, 8.5)	<0.001
CD4+					
Normal	30/266 (11.3)	1.0	Reference	1.0	Reference
Low	159/683 (23.3)	2.4 (1.6,3.6)	<0.001	3.7 (1.5, 8.7)	0.004
Province					
Gauteng	448/1664 (26.9)	1.0	Reference	NS*	-
Eastern Cape	40/95 (42.1)	1.9 (1.3, 3.0)	0.002		
Western Cape	30/301(10.0)	0.30(0.20, 0.44)	<0.001		
Mpumalanga	21/56 (37.5)	1.6 (0.94, 2.8)	0.083		
KwaZuluNatal	61/230 (26.5)	0.98(0.72, 1.3)	0.90		
North West	3/4 (75.0)	8.1(0.84, 78.4)	0.070		
Free State	51/205 (24.9)	0.90(0.64, 1.3)	0.53		
Limpopo	3/22 (13.6)	0.43(0.12, 1.5)	0.17		
Nosocomial infection					
No	639/2514 (25.4)	1.0	Reference	NI	-
Yes	18/63(28.6)	1.2 (0.67,2.0)	0.57		

Current smoker No Yes	 637/2486 (25.6) 20/91 (22.0)	 1.0 0.82(0.49,1.4)	 Reference 0.43	 NI	 -
Alcohol use No Yes	 639/2507 (25.5) 18/70 (25.7)	 1.0 1.0(0.59, 1.7)	 Reference 0.97	 NI	 -
Underlying illnesses No Yes	 145/586 (24.7) 274/1107 (24.8)	 1.0 1.0 (0.79,1.3)	 Reference 0.99	 NI	 -
Pitt bacteraemia score <4 ≥4	 388/1683 (23.0) 86/140 (61.4)	 1.0 5.3 (3.7, 7.6)	 Reference <0.001	 1.0 3.4 (1.5,7.9)	 Reference 0.004
Prior antibiotic use (24 hours) No Yes	 499/2122 (23.5) 34/111 (30.6)	 1.0 1.4 (0.95, 2.2)	 Reference 0.088	 NS**	 -
Prior antibiotic use (2 months) No Yes	 274/1433 (19.1) 93/396 (23.5)	 1.0 1.3 (0.99, 1.7)	 Reference 0.055	 1.0 1.9(0.92,3.9)	 Reference 0.085
Cotrimoxazole prophylaxis No Yes	 219/1169 (18.7) 147/737 (20.0)	 1.0 1.1 (0.86, 1.4)	 Reference 0.51	 NI	 -
Penicillin NonS# No Yes	 389/1532 (25.4) 191/722 (26.5)	 1.0 1.1 (0.86, 1.3)	 Reference 0.59	 NI	 -
Ceftriaxone NonS No Yes	 577/2237 (25.8) 3/17 (17.7)	 1.0 0.62(0.18,2.2)	 Reference 0.45	 NI	 -
Cotrimoxazole NonS No Yes	 212/812 (26.1) 368/1442 (25.5)	 1.0 0.97(0.80,1.2)	 Reference 0.76	 NI	 -
Erythromycin NonS No Yes	 478/1907 (25.0) 102/347 (29.4)	 1.0 1.2(0.97, 1.6)	 Reference 0.090	 1.0 1.4(0.62,2.9)	 Reference 0.44

*NI: Factors not significant on univariate analysis (P>0.10) were omitted in logistic regression model.

**NS: Factors not significant on multivariate logistic regression analysis

NonS: *Streptococcus pneumoniae* isolates not susceptible to the mentioned

[f] Case Fatality Rate: Number of deaths /Number of patients (%). Number of deaths included only those who died within 30 days of admission.

3.16 Summary of the results

The study has shown that age of the patient (<1 year and ≥45 years), province the patient lived in (Eastern Cape, Limpopo and Mpumalanga), severity of illness (Pitt bacteraemia score ≥4), HIV infection, meningitis and prior antibiotic use within 2 months before an episode of IPD were statistically significant risk factors associated with death in patients with invasive pneumococcal disease. Amongst HIV-positive patients severe immunosuppression (low CD4+) was a risk factor for death. Risk factors for death were similar in patients with other IPD and meningitis except for HIV which was associated with death in the meningitis group but not in the other IPD group. Antibiotic resistance and vaccine-serotypes disease were not associated with increased risk of death.

CHAPTER 4

Discussion

4.1 Introduction

We examined in detail several factors that could possibly predict mortality in invasive pneumococcal disease patients in South Africa. The overall mortality of 28% was not substantially different from the 28% and 30.5% reported from previous studies done in the USA and Spain (10;29), however data from Sweden documented rates as low as 7% in adults admitted in the late 1970s.(30) Adjusting for all potential confounders in a multivariate logistic regression analysis, the following factors were significantly associated with mortality: age of the patient (<1 year and ≥45 years) province the patient lived in (Limpopo and Mpumalanga were associated with increased likelihood of dying, while Western Cape was associated with decreased likelihood of dying), acute severe illness (Pitt bacteraemia score ≥4), HIV infection, meningitis and prior antibiotic use within 2 months before admission with an episode of IPD.

Separate analyses of risk factors in the meningitis and other invasive pneumococcal disease groups showed that HIV infection was a significant risk factor for death in pneumococcal meningitis but not in patients with other invasive pneumococcal disease. All other risk factors were the same in both groups and in the overall group of patients with IPD. CD4 + count indicative of severe immunosuppression in IPD patients with HIV co-infection was a significant risk factor for mortality. Antibiotic resistance and vaccine-serotype disease were not associated with mortality.

4.2 Representativeness of the study sample

The populations included in the multivariate analysis were patients from enhanced sites with completed CRFs and available data on outcome. We compared cases from enhanced sites to those from non-enhanced to assess whether the population

eligible to be included (those from enhanced sites) differed from those at non-enhanced sites.

There were significant differences in the proportion of cases from these sites, with greater proportions of young age reported from enhanced sites. This could be because enhanced sites are situated in urban areas where doctors are more likely to take blood cultures from young children than in rural areas. The proportion of cases by province was also significantly different between enhanced and non-enhanced sites. This might be due to the fact that enhanced sites in these provinces are mostly in the urban settings, which have bigger hospitals, and dense populations. A greater proportion of cases are in this setting in some provinces.

There was significant difference in the proportion of specimens from blood or CSF between enhanced and non-enhanced sites. An explanation for this could be that clinicians in more rural areas are less likely to do blood cultures. The proportion of antibiotic resistance differed between enhanced and non-enhanced sites with greater proportions of antibiotics resistance noted in enhanced sites. The reason might be due to high utilization of antibiotics in urban settings where the enhanced sites are situated compared to non-enhanced sites, which are mostly in rural setting. Such differences are consistent with enhanced sites being in larger hospitals in urban areas. (Appendix 1) In summary, the population of patients from enhanced sites does seem to differ from those from non-enhanced sites in age, antibiotic resistance, provincial distribution etc. This may limit generalizability of findings to patients in rural areas.

Since our main interest was analysis of IPD outcome, we focused on data from enhanced sites with completed case report forms and available data on mortality. The reason being mortality data was unreliable in patients without completed CRFs. Cases with completed case report forms did not appear to be different from cases without case report forms except with regard to proportion of specimens from blood or CSF and provincial distribution. Even though our study sample was non-random,

it appears homogeneous and relatively representative of all patients admitted to enhanced sites. Therefore it is unlikely that the validity of our findings of risk factors for death in IPD would be affected.

4.3 Systematic overview of study findings

4.3.1 Meningitis a risk factor for death

Pneumococcal meningitis was significantly associated with an increased risk of dying compared to other invasive disease. A previous study that evaluated risk factors associated with mortality did not find meningitis as a significant risk factor for death on multivariate analysis.(27) Bacteraemic pneumococcal pneumonia constituted 80% of cases of other invasive disease. The case fatality rate for meningitis was 45%, which is higher than previously reported rates of 21 -30 % from North America and Europe, but lower than 58% which was previously reported from South Africa.(2;31-33) In the evaluation of association with mortality some studies have excluded meningitis and have mostly looked at the association between bacteraemic pneumococcal pneumonia and death.(22;31)

4.3.2 HIV co-infection as a risk factor for death in pneumococcal meningitis

Data for HIV was available for 61% of our study sample; of this 87% were HIV co-infected. Our study found that HIV co-infection did not increase the risk of dying with pneumococcal bacteraemia. This is consistent with findings reported from previous studies.(10; 31) However, our study found a significant association between HIV co-infection and increased risk of dying with meningitis. This finding has not been reported before from other studies. This is an important finding in an area where approximately 5.5 million people are living with HIV and where antiretroviral treatment (ARV) scaling up program is taking shape.(34) This should help clinical decision making in comprehensive care plan for such patients including access to antiretroviral treatment.

4.3.3 Low CD4+ count a risk factor for death in IPD with HIV co-infection

To evaluate whether CD4+ count indicative of severe immune deficiency is a predictor of mortality we performed an analysis restricted to IPD patients with HIV co-infection. We found that those with CD4+ count indicative of severe immune deficiency were more likely to die. This finding has not been reported before in South Africa. Thus with the antiretroviral (ARV) scale up program we believe that allowing this group of patients free access to ARV would substantially improve the quality of life and decrease mortality.(22)

4.3.4 Pitt bacteraemia score ≥4 as a predictor of mortality

The presence of acute severe illness clinically assessed as Pitt bacteraemia score of 4 and/or higher is a factor that consistently predicts mortality from invasive pneumococcal disease. Our stratified analysis by clinical syndrome did not show any difference in the association between this factor and mortality. Clinically this might be an indicator of an overall picture of overwhelming sepsis. These findings are similar to those reported from previous studies.(18;22;25;27)

4.3.5 Risk of death due to IPD differs by province

Our analysis revealed that the risk of death in patients with IPD differs by province. The risk is significantly lower in the Western Cape Province and higher in Mpumalanga and Eastern Provinces compared to Gauteng Province. Even after stratifying the analysis by clinical syndrome, we obtained similar results. Our data could not allow us to find a definitive explanation for this finding. We can however suggest that possible differences in health care services available including access to care and case management in these provinces lead to differential outcome in patients with IPD. Differences in specimen-taking practices may mean that the spectrum of patients included differ between provinces e.g. in some provinces only very sick patients had blood cultures done. This is a unique finding and has not been reported before in South Africa.

4.3.6 Prior antibiotic use within 2 months before admission

Our study found that prior antibiotic use within 2 months before admission was a significant risk factor for mortality. This finding has not been reported before. Previous studies have used data on prior antibiotic use before a patient was admitted to hospital as a marker for antibiotic resistance.(27) Our study did not find an association between antibiotic resistance and mortality. However significant differences were noted in the proportion of patients who had used antibiotics 2 months prior to admission with an episode of IPD compared to those who did not use antibiotics. Such differences were apparent in the distribution of these factors: age, vaccine-serotypes, cotrimoxazole prophylaxis, HIV infection, underlying illness and antibiotic resistance such as penicillin, ceftriaxone, cotrimoxazole and erythromycin. We do not have a clear understanding of the influence of prior antibiotic use on mortality. However our data seems to suggest that such patients were more likely to have been HIV-positive children with possible recurrent infections due to immunodeficiency (35) and therefore at a higher risk of dying.

4.3.7 Age associated with the risk of death

Children less than 1 year and adults ≥ 45 years were more likely to die compared to other age groups. This is consistent with findings reported from other studies. Previous studies have reported a significant association between age ≥65 years and death (22;27;31). Reasons for our finding that the 45–64 year old age group were at increased risk of dying as compared to other age groups are unclear. The fact that those ≥65 years were not at greater risk of dying than the 45-64 year age group could be due to differences in population structure with developed countries having a bigger population of the elderly who have a higher prevalence of underlying illnesses (e.g. cancer) compared to South Africa.

4.3.8 Penicillin non-susceptibility not associated with mortality

There was no association found between antibiotic non-susceptibility and increased risk of mortality in all our models. This finding is consistent with published literature of previous studies done in Korea, Spain, Canada, Sweden etc that found

no association between resistance to antibiotics such as penicillin and death.(12; 22; 36) However, we did not assess discordant/concordant therapy among the patients as we were limited by available data.

4.3.9 Vaccine–serotype IPD not associated with increased risk of death

Our study found that vaccine-serotype IPD was not associated with an increased risk of death. To our knowledge there is no published literature showing an association between vaccine-serotype disease and an increased risk of death.

4.3.10 Underlying illness not associated with mortality

There was no association seen between underlying illnesses and increased risk of death in IPD patients. Studies done in developed countries i.e. the USA, Canada, Great Britain etc have shown an association between underlying illness e.g. diabetes and mortality.(18;22;27) This might be due to differences in the prevalence of chronic diseases between these areas with South Africa experiencing a lower prevalence of such disease. We grouped all underlying diseases together for this analysis, as numbers of patients were too small to assess each one individually.

4.4 Potential Study Biases

4.4.1 Collection of exposure and outcome data

The standard practice in data collection was use of objective data sources e.g. death certificates and medical records. However data on antibiotic use before admission to hospital was collected through person-to-person interviews. Systematic differences might have arisen due to differences in interviewing skills between surveillance officers.

4.4.2 Underestimation of incidence rates

Invasive pneumococcal disease cases captured by the surveillance system might not be representative of all the cases of IPD occurring in South Africa within the study period. It is not common practice to do blood cultures in all febrile illnesses; hence some patients might have been missed. Patients who died at home or in transit to

the hospital and those treated for clinical meningitis in cases of failed lumbar puncture might also not have been captured by the surveillance system. Therefore the incidence rates reported earlier on are certainly an underestimation of the true burden of the disease. Thus surveillance bias might exist in our study.

4.4.3 Bias in risk factor analysis

Underestimation of disease burden might have introduced an erroneous estimation of mortality and associated risk factors in our study. Even though missing data are a common problem with the surveillance system, our sample populations which were cases from enhanced sites with completed case report forms and data on mortality, was quite comparable to cases from enhanced sites without case report forms. Use of strict case definition for exposure and outcome might have helped to minimize information bias. To minimize bias in risk factor analysis we restricted our analysis to patients that died within 30 days after admission.

4.5 Residual confounding

All factors of interest were initially examined in a univariate model to find out if they were associated with increased risk of death. Significant factors at $P \leq 0.1$ were included in the multivariate logistic regression model where each factor controlled for the confounding effect of the other. This method helped to control for the confounding effect of several factors at the same time. Factors significant at $P \leq 0.05$ were then considered significant risk factors for mortality.

Residual confounding effect in the association between the risk factors identified and mortality remains a possibility. We did not examine all factors associated with IPD that could also be risk factors for death such as socioeconomic status and access to health services. This information was lacking in our database. However the strength of the association observed between the identified risk factors and mortality might not have been due to chance or residual confounding.(21)

4.6 Generalizability

There appears to be significant differences between cases from enhanced and non-enhanced sites and our population of interest was cases from enhanced sites. This might limit generalizability of our study findings beyond populations of enhanced sites. The difference in the distribution of cases by province might limit generalizability of our study results to other provinces and more rural areas. In the light of the foregoing facts our findings might only be extrapolated to enhanced surveillance sites.

4.7 Study Strengths

- Our study used national data of laboratory-confirmed cases of IPD to evaluate and determine risk factors for death in invasive pneumococcal disease.
- The large numbers of cases included in our study gave enough power to detect differences in risk factors for mortality that were evaluated.

4.8 Study Limitations

- Detailed data on severity of illness and other clinical indicators of disease severity i.e. mechanical ventilation, Glasgow coma score etc was not available as such we could not make an in-depth analysis of clinical risk factors associated with mortality.
- Our study involved retrospective data analysis using surveillance database. The data was not collected specifically for this purpose as such some parameters of interest were not collected e.g. white blood cell count.
- We did not have data on mortality post admission as such death due IPD might have been underestimated
- We could not be sure that death was due to IPD, death could have occurred due to other conditions. To minimize this we restricted our analysis to death that occurred within 30 days after admission.

- This was an analysis of an existing dataset hence other than knowing the antibiotic the patient received we did not have information on the dosage and the duration of treatment as this was not available. Therefore it was difficult to establish discordant therapy (when the patient is treated with an antibiotic to which the organism is resistant). As such we could not fully examine the association between antibiotic resistance and mortality.
- Data for antibiotic treatment were available only for 2005, and it was therefore not possible to compare antibiotic use between the three years and assess its effect on mortality accordingly.
- There was insufficient data on the number of cases that actually were put on ARV to make a meaningful analysis. This also applied to cases that had viral load results. Analysis of association between CD4+ count and mortality for HIV co-infected children was based on absolute counts, as we did not have sufficient data on CD4+%, which is a more reliable measure.
- We also did not have a sufficient number of HIV-positive meningitis cases with CD4+ count to make a meaningful analysis of the effect of CD4 count on mortality risk in this group.

4.9 Suggestions for further studies.

In view of the findings discussed in this chapter, further research is needed to gain a clear understanding behind the provincial differences in the likelihood of dying from IPD. In addition future studies should investigate:

- The association between mortality and prior antibiotic use within 2 months preceding admission with an episode of IPD.
- The association between low CD4+ and mortality in HIV-positive patients with meningitis
- Risk factors for early (within 2 days) versus late deaths (after 2 to 30 days) to establish if such factors are different.

CHAPTER 5

Conclusions and Recommendations

5.1 Conclusions

In conclusion, we found that the case fatality rate for all IPD was 28%. The case fatality rate was higher for meningitis (45%) than for other IPD (22.5%). Meningitis was significantly associated with death compared to other IPD and that HIV infection was a significant risk factor for death in patients with meningitis and not in patients with other IPD. Children less than 1 year and adults ≥45 years had a higher likelihood of dying compared to other age groups. Province, Pitt bacteraemia score ≥4, and prior antibiotic use within 2 months before admission with an episode of IPD were independently associated with death. Risk factors were similar between meningitis patients and those with other IPD except for HIV infection. CD4+ count indicative of severe immunosuppression was a significant risk factor for death in HIV co–infected patients. No association was observed between antibiotic resistance and vaccine-serotype and the risk of dying.

5.2 Key Points

- The risk of death from IPD is greater in children less than 1 year and adults ≥45 years old.
- The risk of death is greater in patients with meningitis compared to those with other IPD.
- HIV co-infection is a risk factor for death in meningitis and not other invasive disease.
- Low CD4+ count is a significant risk factor for death in HIV co–infected IPD patients.
- Pitt bacteraemia score ≥4 is a significant predictor of mortality in all IPD.
- The risk of death in patients with IPD differs by province.
- Prior antibiotic use within 2 months before admission with an episode of IPD is a risk factor for death

5.3 Summary and Recommendations

In summary, the study findings of risk factors for mortality in patients with invasive pneumococcal disease as outlined above are valid and unlikely to be due to chance, sampling bias or residual confounding. Risk factors for death in patients with IPD in South Africa have not been examined before on a national level since good quality data on laboratory-confirmed IPD were lacking. To our knowledge HIV infection as an independent risk factor for death in pneumococcal meningitis has not been previously evaluated in a multivariate model. Most studies have focused on risk factors for death in bacteraemic pneumococcal pneumonia and HIV infection using either retrospective or prospective data.(17;31)

We feel that our study is unique and provides new information to clinicians and public health practitioners for the identification of populations at risk of death. Clinicians should be aware that while young children particularly under the age of 5 years have higher incidence rates of IPD, those under the age of 1 year carry the greatest risk of death and ought to be managed appropriately to minimize their risk of dying. Public health practitioners should therefore reinforce targeted preventive health services to this age group. This point drives home the importance of considering a pneumococcal conjugate vaccine(13;13;14) for children below the age of five years as part of the national expanded program for immunization (EPI), and patients with an increased risk of IPD e.g. patients with HIV co-infection.

These findings have broader implications on public health policy and government commitment to appropriate health intervention measures such as adequate resource allocation to preventive health services, public health education on early presentation to a health care facility and enhancement of primary health care facilities.

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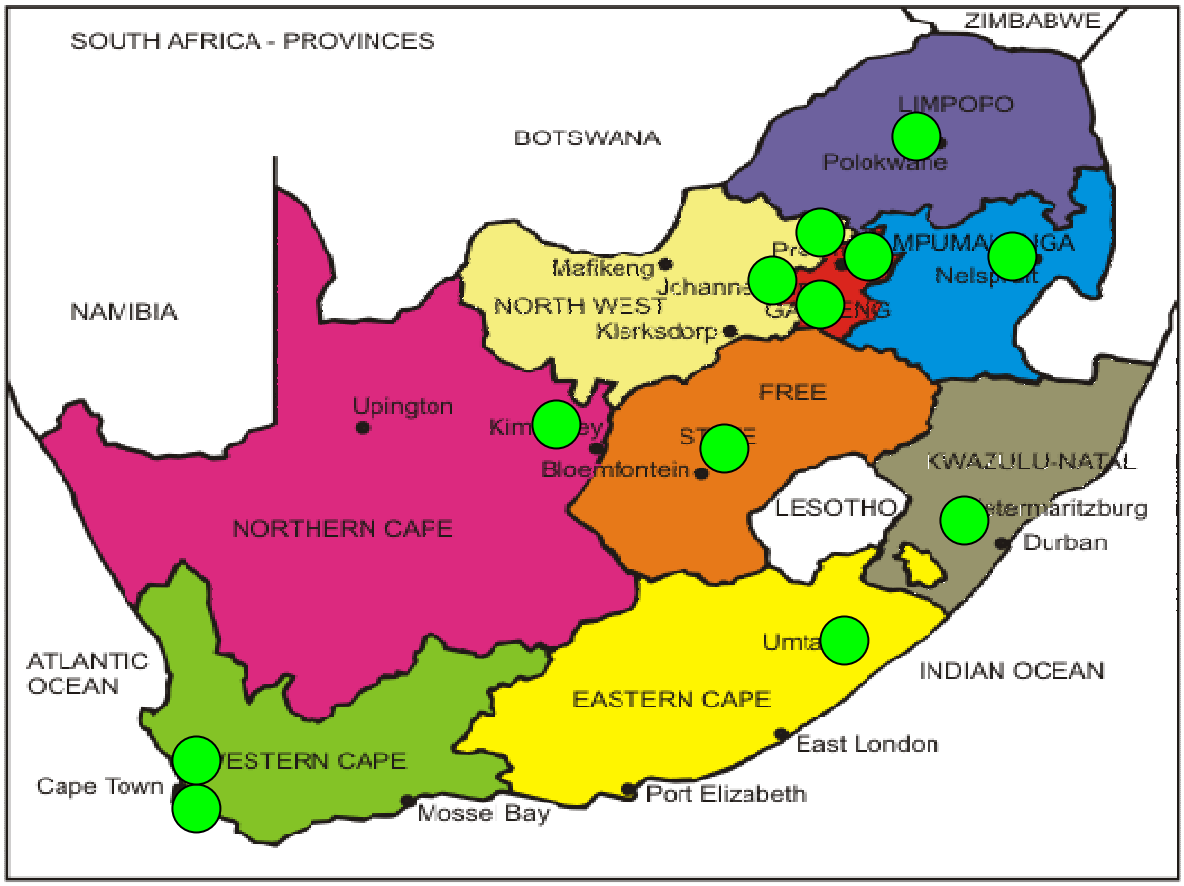
Appendix 1



Map of South African provinces showing enhanced surveillance sites (green circles)

Appendix 2

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Nyasulu

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060906**
PROJECT	Risk Factors for Mortality in Patients with Invasive Pneumococcal Disease in South Africa
INVESTIGATORS	Mr PS Nyasulu
DEPARTMENT	School of Public Health
DATE CONSIDERED	06.09.29
DECISION OF THE COMMITTEE* competed in full and re-submitted	APPROVED subject to ethics application form being

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : C Cohen

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3

Clinical Case Report for Surveillance of Invasive *Haemophilus* spp, *S. pneumoniae*, *N. meningitidis*, *Salmonella* spp, *Shigella* spp., *Cryptococcus* spp.

RESPIRATORY AND MENINGEAL PATHOGENS RESEARCH UNIT **(RMPRU)** TEL: 011 489 9710 / FAX: 011 489 9716

ENTERIC DISEASES REFERENCE UNIT **(EDRU)** TEL: 011 489 9333 / FAX: 011 489 9361

MYCOLOGY REFERENCE UNIT **(MRU)** TEL: 011 489 9341 / FAX: 011 489 9361

Regional Laboratory Specimen Number: ☐☐☐☐☐☐☐☐☐☐ **Laboratory Name:**

Hospital Name:

Hospital Number:	**Ward:**	**Gender:** M ☐ Unk ☐ F ☐	**Race:** Asian ☐ Coloured ☐ Black ☐ White ☐ Unk ☐	**Date of Birth:** d d m m y y y y DOB Unk ☐ **Age:** ☐☐ **Units:** days ☐ months ☐ yrs ☐

Name of Patient: surname: first name: middle initial:

Address: **Town/City:** **Province:**

Tel: (H) **(W)** **(Cell)** **(Neighbour)**

Have you stayed in SA for the last month: Yes ☐ No ☐ Unk ☐ **If no, which country have you come from?**

Date of admission to Acute Hospital: d d m m y y y y

Outcome at Acute Hospital: Transferred ☐ Discharged ☐ Died ☐ RHT/Absconded ☐ Unk ☐

If patient was transferred, name of hospital transferred to: **Date of Transfer:** d d m m y y y y

Final outcome of patient at place of discharge: Discharged ☐ Died ☐ RHT/Absconded ☐ Unk ☐ **Date of final outcome:** d d m m y y y y

DIAGNOSIS

Meningitis ☐ LRTI ☐ Dysentery ☐ Diarrhoea ☐ Fungaemia/Bacteraemia without focus ☐ Other ☐ Specify

Date of specimen collection d d m m y y y y

Site of collection CSF ☐ Blood Culture ☐ Joint Fluid ☐ Other

SPECIES ISOLATED

Haemophilus sp. ☐ *N. meningitidis* ☐ *S. pneumoniae* ☐ *Salmonella* sp. ☐ *Shigella* sp. ☐ *Cryptococcus* sp. ☐

Number of children living with you: (<18 years) None ☐ Number ☐ Place of safety ☐ Unk ☐

Have any of these children been hospitalised recently? (last 3 months) Yes ☐ No ☐ Unk ☐

SEVERITY OF ILLNESS (On the day the positive specimen was taken)

Temperature: ____ °C Fever: Yes ☐ No ☐ Unk ☐ BP: ____ / ____ Unk ☐ Mechanical Ventilation: Yes ☐ No ☐ Unk ☐ Cardiac Arrest: Yes ☐ No ☐ Unk ☐

Mental Status: Alert ☐ Disorientated ☐ Stuporous ☐ Comatosed ☐ Unk ☐ GCS ____ /15 ___ E ___ M ___ V ___ Unk ☐

UNDERLYING DISEASES

HIV STATUS PRIOR TO THIS ADMISSION Positive ☐ Negative ☐ Unknown ☐

HIV STATUS AT THIS ADMISSION Positive ☐ Negative ☐ Unknown ☐

Pre & Post test counselling offered by SO Yes ☐ No ☐

If yes, was HIV consent given to SO Yes ☐ No ☐

If NO HIV taken, is there clinical suspicion of HIV? Yes ☐ No ☐ Unk ☐

Most recent CD4 count: Absolute ; % **Date taken** d d m m y y y y Unk ☐

Most recent viral load: **Date taken** d d m m y y y y Unk ☐

OTHER IMMUNOCOMPROMISE: *(Tick all that apply)* None ☐ Unknown ☐

TB ☐	Current smoker ☐	Emphysema/COPD ☐	Coronary artery disease ☐	Malignancy (specify) ☐
Oral candidiasis ☐	Sickle cell anaemia ☐	Diabetes mellitus ☐	Valvular disease ☐	
PCP ☐	Splenectomy/asplenia ☐	Nephrotic syndrome ☐	Heart failure ☐	Organ transplant (specify) ☐
Wasting secondary to HIV ☐	Immunoglobulin deficiency ☐	Chronic renal failure ☐	Burns ☐	
Chronic diarrhoea > 10 days ☐	Immunosuppressive therapy (Steroids,Chemotherapy,Radiation) ☐	Systemic Lupus Erythematosus(SLE) ☐	Cerebral vascular accident (CVA)/ Stroke ☐	Other (specify) ☐
Kaposis Sarcoma ☐	Kwashiokor/marasmus ☐	Cirrhosis/Liver failure ☐	History of head injury/ head surgery ☐	
	Asthma ☐	Alcohol dependancy ☐	Hydrocephalus with VP shunt ☐	

PREVIOUS ADMISSIONS in last 12 months: Yes ☐ No ☐ Unk ☐ **Number of admissions** ☐☐

page 1 of 3
Revised Jan 2005

Appendix 3

Clinical Case Report for Surveillance of Invasive *Haemophilus* spp, *S. pneumoniae*, *N. meningitidis*, *Salmonella* spp, *Shigella* spp., *Cryptococcus* spp.

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MYCOLOGY REFERENCE UNIT (MRU) TEL: 011 489 9341 FAX: 011 489 9361

Regional Laboratory Specimen Number:

VACCINATION STATUS FOR *STREPTOCOCCUS PNEUMONIAE*

If <15 years of age did patient receive **pneumococcal conjugate** vaccine? Yes ☐ No ☐ Unk ☐ **If YES, please complete the list below**

DOSE	DATE GIVEN (d d m m y y y y)	NAME OF CLINIC
1		
2		
3		

Has patient received **23-valent pneumococcal polysaccharide** vaccine? Yes ☐ No ☐ Unk ☐

If YES, list date most recently given and vaccine name (d d m m y y y y)

HAEMOPHILUS INFLUENZAE

If <15 years of age did patient receive *Haemophilus influenzae* type b vaccine? Yes ☐ No ☐ Unk ☐

DOSE	DATE GIVEN (d d m m y y y y)	NAME OF CLINIC
1		
2		
3		

Was there documented proof of vaccination for: *Haemophilus influenzae* type b (Hib) vaccine? Yes ☐ No ☐ Unk ☐

OTHER VACCINATIONS

Meningococcal vaccine: A/C ☐ A/C/Y/W135 ☐ *Salmonella typhi* vaccine ☐ **Date of vaccination** (d d m m y y y y)

ANTIBIOTICS PRIOR TO THIS ADMISSION

Cotrimoxazole prophylaxis Yes ☐ No ☐ Unk ☐	**Dose:** **Route:**		**Date initiated:** (d d m m y y y y)	**Compliant in last month:** Most ☐ Some ☐ None ☐
ABX in 24 hours before specimen: Yes ☐ No ☐	**Names:** 1 2 3 4	**Dose:** **Route:**		**Date initiated:** (d d m m y y y y)
Other ABX in 2 months Yes ☐ No ☐ Unk ☐	**Names:** 1 2	**Dose:**	**In the last 30 days:** Yes ☐ No ☐	**In the last 30 to 60 days:** Yes ☐ No ☐
TB Rx Yes ☐ No ☐ Unk ☐	**Drugs:** 1 2	**Dose:**	**Date initiated:** (d d m m y y y y)	**Compliant is last month:** Most ☐ Some ☐ None ☐

ANTIBIOTIC USE IN HOSPITAL DURING THIS ADMISSION (excluding TB therapy)

	Name of antimicrobial	Dose	Route	Date initiated (d d m m y y y y)	Total doses given/no. of days
1					
2					
3					
4					
5					

ANTIRETROVIRAL USE

Any antiretroviral use? Yes ☐ No ☐ Unk ☐ If Yes: Current ☐ Previous ☐ Perinatal ☐ Unk ☐

Current Antiretroviral therapy: 3TC ☐ D4T ☐ Efavirenz ☐ Nevirapine ☐ AZT ☐ DDI ☐ Kaletra ☐ Unk ☐ Duration: Months

Appendix 3

Clinical Case Report for Surveillance of Invasive *Haemophilus* spp, *S. pneumoniae*, *N. meningitidis*, *Salmonella* spp, *Shigella* spp., *Cryptococcus* spp.

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MYCOLOGY REFERENCE UNIT (MRU) TEL: 011 489 9341 ✐ FAX: 011 489 9361

ANTIFUNGALS PRIOR TO THIS ADMISSSION (For crypto isolates ONLY)

		Date initiated	Dose:
Fluconazole:	Yes ☐ No ☐ Unk ☐	If yes d d m m y y y y	
Amphotericin B	Yes ☐ No ☐ Unk ☐	If yes d d m m y y y y	

ANTIFUNGALS DURING THIS ADMISSSION

	Dose	Route	Date initiated	Total doses given/no. of days
Fluconazole:			d d m m y y y y	
Amphotericin B			d d m m y y y y	

On **discharge** was the patient given fluconazole? Yes ☐ No ☐ Unk ☐

Sources of data: Patient/Guardian ☐ Clinician ☐ Medical Records ☐

Has regional laboratory sent isolate to RMPRU/EDRU/MRU Yes ☐ No ☐ **Date isolate sent** d d m m y y y y

SURVEILLANCE OFFICER NAME: