INVASIVE PNEUMOCOCCAL DISEASE IN NEONATES
PRIOR TO PNEUMOCOCCAL CONJUGATE VACCINE
USE IN SOUTH AFRICA: 2003 – 2008

By

Krishnee Moodley (MBChB) (FCPath SA(Micro))

Submitted in partial fulfillment of the academic requirements for the degree MMed (Micro), in the Department of Microbiology, School of Laboratory Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, 2018

As the candidate's supervisors we have approved this thesis for submission

Name: Prof Y Coovadia                 Prof Anne von Gottberg

Signed: __________________________    Signed: __________________________

Date: 15 March 2018                  Date: 15 March 2018

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Name: Prof Y Coovadia
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Date: 15 March 2018
Date of submission: 15 March 2018

Prof Anne von Eiff
Signed:  
Date: 15 March 2018
DECLARATION:

I, Krishnee Moodley, declare that:

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

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(iii) This dissertation does not contain other persons' data, pictures, graphs, or other information, unless specifically acknowledged as being sourced from other persons.

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# TABLE OF CONTENTS

**DECLARATION:** ........................................................................................................... iii  

**ACKNOWLEDGEMENTS:** ................................................................................................. v  

**CHAPTER 1: LITERATURE REVIEW** ............................................................................... 1  

**CHAPTER 2: MANUSCRIPT** ............................................................................................ 10  

**CHAPTER 3: REFERENCES** ............................................................................................... 49  

**CHAPTER 4: APPENDICES** ............................................................................................... 55
CHAPTER 1: LITERATURE REVIEW

Introduction

The global under five mortality rate was estimated to be 43 per 1000 live births in 2015. The highest rate was noted in Sub Saharan Africa, with infectious diseases implicated as the leading cause of mortality in children under 5 years of age [1]. Pneumonia was the second commonest cause of death in children under 5 years of age [1]. *Streptococcus pneumoniae* accounted for approximately 11% of childhood deaths in the under five-year age group, worldwide [2]. This encapsulated Gram-positive diplococcus is the commonest bacterial cause of pneumonia, otitis media, septicemia and meningitis in this age group [3].

Invasive pneumococcal disease (IPD) is defined as “morbidity associated with the isolation of pneumococci from a normally sterile body site, such as the blood stream, or those secondary to blood stream spread, e.g. meningitis or septic arthritis” [4]. Incidence rates for IPD are highest in young children (<2 years of age) and the elderly > 65 years, in patients with chronic illnesses such as cardiac failure and chronic obstructive pulmonary disease, as well as HIV infection and splenectomy [5].

In South Africa, HIV infection has been reported to be a significant risk factor for IPD in children and adults [6, 7].

**Invasive pneumococcal disease in the neonate**

The first known case of IPD in a neonate was reported in 1889 in Paris [8]. Since then several case series and case reports have described neonatal IPD in different parts of the world [8, 9]. Billings *et al* reported an estimated global incidence of 36 per 100 000
live births, at a time when most countries had not introduced the pneumococcal vaccine into their childhood immunization programs [10]. In their analyses, they observed that there was a paucity of data on neonatal IPD in low- to middle-income countries (LMICs) [10]. The incidence of neonatal IPD in South Africa has not previously been documented.

**Clinical features and outcome**

Neonatal sepsis is defined as “early-onset” if it occurs at <7 days of age and “late-onset” if it occurs at ≥ 7 < 28 days of age [11]. Early-onset disease (EOD) in neonates may be acquired *in utero* by hematogenous spread or intrapartum, either by ascending infection or during passage through the birth canal in the presence of vaginal colonization [12, 13]. Late-onset disease (LOD) is acquired postnatally via horizontal spread from the mother, family members or other caregivers [12, 13].

In one of the largest case series of neonatal IPD, Gomez *et al* reported a preponderance of early-onset disease [8]. This was similar to the findings by Geelen *et al* in the Netherlands [14], and Soto-Noguerón *A et al* in Mexico [15]. In contrast, Hoffman *et al* reported on a series of 29 neonates with IPD wherein they found that most cases presented in the third week of life [9] (Table 1). These differences may be due to differences in at-risk populations, socio-economic conditions and access to maternal and child healthcare [15].

The clinical presentation of IPD in neonates included pneumonia, meningitis, bacteremia, otitis media and osteomyelitis [8, 9, 16]. Sepsis was reported to be the predominant clinical presentation in the early-onset group and meningitis in the late-onset group [9]. Neonatal IPD was associated with a high mortality rate, up to 50% in
one case series [14, 16] (Table 1), with the reported case fatality ratio being highest in
the early-onset group [8].

The risk for IPD among children < 1 years of age has been found to be greater in HIV-
infected than HIV-uninfected children in South Africa [6]. The risk for IPD was also
found to be higher among infants <6 months of age who were HIV-exposed but not
infected, compared to those who were HIV-unexposed and uninfected, in South Africa
[17]. This increased risk may also be present among neonates, but has not been
reported to date, in South Africa or in other parts of the world.

Serotype distribution

Based on the capsular polysaccharide antigen, there are >90 S. pneumoniae serotypes
[18]. The serotypes differ in terms of their ability to colonize the nasopharynx, cause
invasive disease, association with clinical syndromes, antimicrobial resistance patterns,
preponderance in different age groups as well as ability to cause outbreaks [19].

“Pediatric” serotypes have been described as those serotypes most frequently isolated
from children <5 years old and most frequently associated with antimicrobial resistance
[19]. These include serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F (PCV7 serotypes) as
well as serotypes 6A and 19A [19].

The most frequently isolated serotypes prior to the introduction of the pneumococcal
conjugate vaccines into national immunization schedules were the seven serotypes
included in the seven valent pneumococcal conjugate vaccine (PCV7). These seven
serotypes, 4, 6B, 9V, 14, 18C, 19F, and 23F, accounted for 60 – 75% of IPD in children
in different parts of the world [6, 20]. In 2010 vaccines providing coverage against
additional serotypes, the 10-valent (PCV10) and 13-valent (PCV13) vaccines, were
The PCV7 was introduced as part of the routine pediatric immunization schedule in South Africa in 2009. However, in 2011 the PCV7 was replaced by the PCV13, which added serotypes 1, 3, 5, 6A, 7F, 19A to the serotypes covered.

In England, prior to PCV introduction, the serotypes implicated in neonatal IPD were reported to be those more frequently isolated in older children and young adults [22]. In infants <90 days of age PCV 7 and PCV 13 serotypes accounted for 44% and 63% of serotyped isolates in the same study [22]. Similar coverage was noted in Mexico in children <=60 days of age, also in the prevaccine era [15]. Hoffman et al reported 75% of IPD was due to PCV 7 serotypes, in the USA [9]. The most frequent serotypes in neonatal IPD were 1, 3, 5, 12, 7F, 19F [9, 15, 20] (Table 1). These are all vaccine serotypes included in the PCV13. However, serotypes 3, 5 and 7F have been reported as uncommon causes of IPD in South African children < 5 years of age [6].

Neonates may be protected from IPD by the indirect effects of PCV, or by maternal immunization. Herd protection with use of PCV occurs through vaccinated individuals who are less likely to carry vaccine-type pneumococci, thus reducing transmission and conferring protection to those who are unimmunized [23]. The decrease in neonatal IPD in England and Wales post-PCV introduction suggests a role for herd protection [22]. Maternal immunization strategies have been explored by investigators in Brazil [24, 25]. However, there is no current recommendation for routine immunization of pregnant mothers against pneumococcus, as there is insufficient evidence that such vaccination confers protection to the neonate [26, 27].
Antimicrobial susceptibility

The first clinical isolate of penicillin non-susceptible *S. pneumoniae* was reported in 1967 in Papua, New Guinea [28]. Since then numerous reports have documented the clonal spread of multidrug-resistant *S. pneumoniae*, in South Africa, as well as globally [29, 30]. On a global level, the serotypes associated with penicillin resistance were 19A, 19F, 35B, 6A, 6B, 23A, 9V, 15A, and 14 [31]. Multidrug-resistance (MDR) is defined as resistance to antimicrobials in three or more classes [32]. In 2008, the incidence of MDR IPD was highest in the <1-year age group [6]. In South Africa, prior to the introduction of the conjugate vaccines, the strongest independent risk factor for multidrug resistant IPD was IPD caused by PCV13 serotypes [33].

In contrast, neonatal IPD has been associated with penicillin-susceptible isolates (Table 1). This has been attributed to the fact that the commonest serotypes implicated in neonatal IPD are infrequently associated with antimicrobial resistance [8, 9, 22].

International guidelines for empiric therapy of suspected neonatal sepsis include the use of ampicillin and gentamicin, or a third generation cephalosporin [34]. Such regimens would therefore provide adequate coverage for neonates with IPD.
Summary

Neonatal IPD has been well-described in high-income countries, but there is a paucity of data in LMICs. This is the first study in South Africa that aims to provide baseline data on the pre-vaccine incidence, clinical features, serotype distribution and antimicrobial susceptibility of neonatal IPD. This study provides a background upon which to interpret changes that may occur in the post-vaccine era in neonates. This study also provides useful baseline data for other LMICs who are still rolling out the PCV in their countries.
<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Design</th>
<th>Study population</th>
<th>EOD % (n)</th>
<th>LOD % (n)</th>
<th>PCV7% (n)</th>
<th>PCV13% (n)</th>
<th>Predominant serotypes</th>
<th>Penicillin susceptibility % (n)</th>
<th>Case fatality ratio (CFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez M <em>et al</em> [8]</td>
<td>Ohio, USA</td>
<td>1966-1998; Case reports and literature review; IPD, Age &lt;30 days</td>
<td>101</td>
<td>86(87)</td>
<td>14(14)</td>
<td></td>
<td></td>
<td>3, 19</td>
<td></td>
<td>48(46)</td>
</tr>
<tr>
<td>Hoffman JA <em>et al</em> [9]</td>
<td>USA</td>
<td>1993 – 2001; Pediatric Multicentre Pneumococcal Surveillance Group; IPD, age ≤30 days</td>
<td>21</td>
<td>14(3)</td>
<td>86(18)</td>
<td>75(15)</td>
<td></td>
<td>1, 3, 5, 12, 19</td>
<td>80(16)</td>
<td>14(3)</td>
</tr>
<tr>
<td>Malhotra A <em>et al</em> [12]</td>
<td>Melbourne, Australia</td>
<td>2 years, 3 hospital sites</td>
<td>4</td>
<td>100(4)</td>
<td>0</td>
<td>25(1)</td>
<td>50(2)</td>
<td></td>
<td>50(2)</td>
<td>0</td>
</tr>
<tr>
<td>Geelen SBM <em>et al</em> [14]</td>
<td>The Netherlands</td>
<td>1975 – 1988; Neonatal ICU</td>
<td>7</td>
<td>100(7)</td>
<td>0</td>
<td></td>
<td></td>
<td>3, 19</td>
<td></td>
<td>43(3)</td>
</tr>
<tr>
<td>Soto-Noguerón A <em>et al</em> [15]</td>
<td>Mexico</td>
<td>2000 -2014; National, PCV7 introduced in 2006; IPD and NIPD, age &lt; 60 days</td>
<td>IPD = 69</td>
<td>26 (18)</td>
<td>74 (51)</td>
<td>34 (43)</td>
<td>64 (80)</td>
<td></td>
<td></td>
<td>13 (7)</td>
</tr>
<tr>
<td>Author</td>
<td>Setting</td>
<td>Design</td>
<td>Study population</td>
<td>EOD</td>
<td>LOD</td>
<td>PCV7a</td>
<td>PCV13b</td>
<td>Predominant serotypes</td>
<td>Penicillin susceptibility</td>
<td>Case fatality ratio (CFR)</td>
</tr>
<tr>
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<tr>
<td>Kaltoft M et al</td>
<td>Denmark</td>
<td>1981-1999; National surveillance; IPD, age &lt; 1 month</td>
<td>44</td>
<td>30</td>
<td>90</td>
<td>1, 3, 19F, 4, 5, 7F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladhani SN et al</td>
<td>England and Wales</td>
<td>1998 -2010; Health Protection Agency (HPA) IPD surveillance, age &lt;30</td>
<td>480</td>
<td>74</td>
<td>26</td>
<td>22</td>
<td>98</td>
<td>98(91)</td>
<td>9(12)</td>
<td></td>
</tr>
<tr>
<td>Hans-Christian</td>
<td>Denmark</td>
<td>1943 – 2013; National, PCV7 introduced 2007; IPD, age &lt; 90 days</td>
<td>216</td>
<td>33</td>
<td>67</td>
<td>1, 7F, 19F, 3, 8F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slotved et al [35]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18C and 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poehling KA et al [36]</td>
<td>USA</td>
<td>1997-2004; Eight states in the USA; PCV7 introduced in 2000; IPD, age 0-90 days</td>
<td>146</td>
<td>68</td>
<td>32</td>
<td>38</td>
<td>57</td>
<td>6B, 19F, 23F</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

Note: EOD = Early onset disease; LOD = Late onset disease; PCV7a = PCV7 serotypes; PCV13b = PCV13 serotypes; CFR = Case fatality ratio.
Table 1: Summary of neonatal invasive pneumococcal disease in different countries, 1975 – 2013

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Design</th>
<th>Study population</th>
<th>EOD</th>
<th>LOD</th>
<th>PCV7&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PCV13&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Predominant serotypes</th>
<th>Penicillin susceptibility</th>
<th>Case fatality ratio (CFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagos R et al [37]</td>
<td>Santiago, Chile</td>
<td>1994 – 2007; Metropolitan region; IPD, age 0 - 5 months</td>
<td>430</td>
<td></td>
<td></td>
<td>1, 5, 14, 19F;</td>
<td>19A</td>
<td>13(57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bas AY et al [38]</td>
<td>Turkey</td>
<td>1999 – 2008: Tertiary hospital ICU – pneumococcal meningitis, age &lt; 30 days</td>
<td>8</td>
<td>13(1)</td>
<td>87(7)</td>
<td>100(8)</td>
<td>50(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olarte et al [39]</td>
<td>Utah</td>
<td>1997-2010; Single tertiary children’s hospital; PCV7 introduced 2001; IPD, age 1 - 90 days</td>
<td>36</td>
<td>33(2)</td>
<td>67(4)</td>
<td>19(7)</td>
<td>69(25)</td>
<td>7F</td>
<td>50(3)</td>
<td></td>
</tr>
<tr>
<td>Mount V et al [40]</td>
<td>New Zealand</td>
<td>2009 – 2013; National surveillance; IPD; PCV7 introduced in 2008; age &lt;90 days</td>
<td>29</td>
<td>47(9)</td>
<td>53(10)</td>
<td>26(5)</td>
<td>74(14)</td>
<td>19F, 19A, 3</td>
<td>89(17)</td>
<td>11(1) &lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Footnotes:

Abbreviations – IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; EOD = early-onset disease (<7 days old); LOD = late-onset disease (≥7–28 days old); CFR = case fatality ratio; ICU = intensive care unit

a - seven-valent PCV; b – thirteen-valent PCV; c – NIPD = non-invasive pneumococcal disease; d – EOD was aged 0-10 days; e - LOD was >10-<89 days; f - only EOD outcome was reported in this study
CHAPTER 2: MANUSCRIPT

Title: Invasive pneumococcal disease in neonates prior to pneumococcal conjugate vaccine use in South Africa: 2003 – 2008

This manuscript has been prepared according to the instructions for authors for submission to Pediatric Infectious Diseases Journal (PIDJ). The manuscript has been reviewed by PIDJ reviewers and corrections have been made. A revised manuscript has been submitted to PIDJ and I am currently awaiting feedback from the editors.

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Keywords: Neonates, invasive pneumococcal disease, South Africa, *Streptococcus pneumoniae*, pneumococcal conjugate vaccine

Cover title: Neonatal IPD in South Africa in the pre-vaccine era: 2003-2008

**Abstract**

Background: Neonatal invasive pneumococcal disease (IPD) in developing countries is poorly described. We provide a baseline description of neonatal IPD in South Africa, prior to implementation of the seven-valent pneumococcal conjugate vaccine (PCV7) in 2009.

Methods: Data from children (age ≤ 2 years) with IPD (pneumococcus identified from a normally sterile specimen) from January 2003 - December 2008 were extracted from a national laboratory-based surveillance database. Clinical and laboratory characteristics of IPD amongst neonates (0-27 days old) was compared to IPD amongst young children (≥28 days ≤ 2 years). Early-onset IPD (EOD) (0 - 6 days old) was compared with late-onset IPD (LOD) (≥7 – 27 days old). Isolates were serotyped using the Quellung reaction.

Results: Overall 27 630 IPD cases were reported. Of the 26 277 (95%) with known ages, 6583 (25%) were ≤ 2 years of age, of which 4.5% (294/6583) were neonates. The estimated annual incidence of neonatal IPD in 2008 was 5 per 100 000 live births. Fifty-one percent of neonates with IPD presented with EOD. Case-fatality ratios (CFR) were high in both groups, 31% (28/89) in neonatal IPD vs 26%(614/2383) in non-neonatal IPD (p=0.18). Among neonates the meningitis cases (15/37, 41%) were associated with the highest CFR. The thirteen-valent pneumococcal conjugate vaccine (PCV13) serotypes accounted for 69% (134/194) of neonatal IPD isolates.

Conclusions: Pneumococcal neonatal disease in South Africa was not uncommon prior to PCV introduction, and is associated with a high CFR. The indirect effect on neonatal IPD of PCV rollout requires further evaluation.

**Introduction**

Invasive pneumococcal disease (IPD) is a significant cause of mortality and morbidity in children under five years of age, with the highest incidence (an estimated 75% of reported cases) in children ≤ two years of age [1, 2]. An estimated 6 – 8% of globally reported IPD in children under five years of age occurred in under two month old infants [3].

The estimated global incidence of neonatal IPD in 2010 was 36 per 100 000 live births, when many low-income countries were still not using the pneumococcal conjugate vaccine (PCV) [4]. This incidence however, varies markedly from low- and middle-income countries (LMIC) such as Chile, with an incidence of 59 per 100 000 population [5], and high-income countries such as the USA and England and Wales, with an incidence of 11 – 13 per 100 000 live births [6, 7]. The incidence of neonatal IPD in South Africa, a middle-income country with a high maternal HIV infection rate, is not known [8].

Neonates are at risk for IPD via exposure to *Streptococcus pneumoniae* either during passage through the birth canal, by hematogenous spread *in utero*, or by horizontal spread from caregivers and siblings [9, 10]. Neonatal IPD has been categorized as early-onset disease (EOD) or late-onset disease (LOD) based on presentation in the first seven days of life or later [11]. The presenting clinical features are non-specific [12]. Neonatal IPD isolates are reported to be more susceptible to antimicrobials than those found in older children [13]. The case fatality ratio (CFR) in neonatal IPD may be high, up to 50% [12].
The seven-valent PCV (PCV 7) was introduced into the routine immunization schedule in South Africa in 2009, and replaced by the thirteen-valent PCV (PCV13) in 2011. Globally, most of the serotypes in neonatal IPD, serotypes 1, 3, 5, 12, 7F, are included in the PCV13 [13, 14]. Herd protection with use of PCV occurs through vaccinated individuals who are less likely to carry vaccine-type pneumococci, thus reducing transmission and conferring protection to those who are unimmunized [15]. Neonates may be protected by maternal antibodies or by the indirect effects of PCV. There is currently no recommendation for routine immunization of pregnant mothers against pneumococcus [16,17]. The serotype distribution of neonatal IPD in South Africa and other developing countries prior to the introduction of PCV is largely unknown [4].

This study describes neonatal IPD, in the pre-PCV era, in South Africa, with the aim of providing baseline data to assist the interpretation of changes, with respect to incidence, serotype distribution, clinical presentation, and antimicrobial susceptibility, that may have occurred since the introduction of PCV. In view of the lack of pre-vaccine data on neonatal IPD in LMICs, the findings in this study are also of value to other countries who are still in the introductory phases of PCV implementation [4].
Methods

Ethics

Ethical clearance was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE 012/010). In addition, ethical clearance and permission to conduct laboratory-based and enhanced surveillance in South Africa for this study was obtained from the Health Research Ethics Committee (Human), University of Witwatersrand (Clearance number M02-10-42); the University of Stellenbosch Health Research Ethics Committee (Reference number N04/01/0021), the National Institute for Communicable Diseases Research Committee (Clearance number M060449); and the South African Department of Health (Reference H2/12/8).

Surveillance

Surveillance data were extracted from an ongoing, active, laboratory-based surveillance system, performed through GERMS-SA (Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa), commencing in 1999 and enhanced in 2003 [18]. GERMS-SA is a national laboratory-based surveillance system that collects data and isolates from both the public and private sector laboratories in South Africa. Their enhanced surveillance sites employ surveillance officers who perform follow-up on reported cases and populate case report forms (CRFs) with additional data such as admission dates, clinical diagnosis, outcome and HIV status. The enhanced surveillance (ES) stabilized in 2005, and continued through 2008. Reports and pneumococcal isolates from individuals with laboratory-confirmed IPD were submitted from > 130 laboratories (public and private sector) nation-wide to the National Institute for Communicable Diseases (NICD) in Johannesburg, South Africa. Each report

contained patient demographic data including age, sex, date of specimen collection and specimen type. Additional information including admission date, HIV status, clinical diagnosis, and outcome were collected only at the ES sites, 25 hospital-based laboratories in the nine provinces. Surveillance officers documented outcome as in-hospital mortality, or recovery. Transferred cases were followed up. Outcomes were unknown where children were removed from the hospital by caregivers prior to discharge or where it was inadvertently not documented. Audits were performed using a laboratory information system (LIS) for the public sector laboratories (80% of healthcare in South Africa), where all cases satisfying the case definition not already reported to the surveillance system were added to the database.

Definitions

IPD cases were defined as all children with a known age of ≤ 2 years with *S. pneumoniae* isolated from a normally sterile body site specimen, such as cerebrospinal fluid (CSF), blood, pleural and joint fluids, from January 2003 through December 2008, in South Africa. Individuals who presented within 21 days with a second episode of IPD were excluded.

Neonates were defined as infants 0 – 27 days of age. We compared the characteristics of IPD in neonates with non-neonates (28 days to ≤ 2 years of age), the age group associated with the highest incidence of IPD.

Early-onset disease (EOD) was defined where the specimen collection date was at age <7 days old, while late onset-disease (LOD) included all neonates with a specimen collection date at ≥ 7 - 27 days of age [19].
Specimen source was defined according to the specimen type positive for pneumococcus as follows: CSF specimen, irrespective of any other specimen; blood specimen irrespective of other specimen type (excluding CSF); and “other” including all other normally sterile specimen types (excluding blood and CSF specimens).

Clinical syndromes, available from ES sites only, were defined as: meningitis, as documented in clinical notes or if the IPD specimen was CSF; lower respiratory tract infection, as documented in clinical notes, together with culture of an isolate from a sterile site (including blood, pleural fluid); bacteremia without focus, where a focus was not documented and the specimen was blood; “other” included all cases not included in the definitions above.

“Pediatric” serotypes were defined as serotypes 6B, 9V, 14, 19F, and 23F. These have been defined as a group of serotypes associated with increased antimicrobial resistance and frequently isolated from children [20].
Incidence rates

Incidence rates were calculated using the number of reported cases of IPD with known ages for each group as the numerator. The denominator for neonates was live births for each year, while that for the non-neonates was the number of one-month-old children subtracted from the mid-year population estimates for ≤ 2-year-old children, for each year. The population estimates were extracted from Statistics South Africa [21]. Incidence was reported per 100 000 population.

Microbiology and serotyping

Identification of the submitted pneumococcal isolates was confirmed at the NICD using standard microbiological techniques i.e. colony morphology, haemolysis and optochin susceptibility. Serotyping was performed with the Quellung reaction, using specific pneumococcal antisera (Statens Serum Institut, Copenhagen, Denmark). The serotypes included in PCV7 are 4, 6B, 9V, 14, 18C, 19F and 23F. PCV10 includes three additional serotypes: 1, 5, 7F, and PCV 13 an additional 3: 3, 6A, 19A [2].

All isolates were screened for penicillin resistance by disk diffusion testing using a 1µg oxacillin disk (Mast diagnostics, Merseyside, United Kingdom). Isolates testing non-susceptible on screening had minimum inhibitory concentrations (MICs) determined by agar dilution or Etest® (AB-Biodisk, Solna, Sweden) for penicillin and ceftriaxone. Isolates were also tested against the following agents using the disk diffusion method: erythromycin, clindamycin, chloramphenicol, tetracycline, rifampicin, cotrimoxazole and ofloxacin - if non-susceptible, MICs were determined by Etest®. Results were interpreted using Clinical and Laboratory Standards Institute (CLSI) 2013 guidelines [22]. Isolates were considered non-susceptible to penicillin at MICs ≥ 0.12 mg/L using
the parenteral penicillin meningitis breakpoints. For other antimicrobial agents, isolates were defined as non-susceptible if they were intermediately or fully resistant to the agent tested. Multidrug-resistance (MDR) was defined as non-susceptibility to at least one agent in three or more different classes [23].

The recommendation for HIV testing at the time of the study was to perform a qualitative DNA polymerase chain reaction for children < 18 months of age and an enzyme linked immunosorbent assay (ELISA) for children ≥ 18 months of age [24], as requested by the attending clinician.

**Statistical analysis**

Medians and interquartile ranges are presented for continuous variables and frequencies are presented for categorical variables. Chi-square tests are used to compare groups. A $p$ value (2-tailed) of ≤ 0.05 was considered significant. Epi Info™ version 7.2.1.0 was used to analyse the data.
Results

Demographics

There were 27,630 reported IPD cases from January 2003 through December 2008, 26277 (95%) with known ages, of whom 25% (6,583) were aged ≤ 2 years, and 4.5% (294/6,583) of these were neonates. Forty-two percent (2,747/6,583) of IPD cases were from ES sites, which included 31% (92/294) neonates and 42% (2,655/6,289) non-neonates ($p < 0.01$) (Table 1). In 2008, the national incidence of neonatal IPD was 5 per 100,000 live births, 22-fold lower than the non-neonatal incidence of 110 per 100,000 population (Figure 1). The change in incidence was relatively stable from 2003 – 2008 among both neonates and non-neonates ($p = 0.05$) except for a peak in neonatal incidence in 2007 (from 44 cases in 2006 to 70 cases in 2007) (Figure 1). There was no spatial or serotype clustering among these cases.

Although there was some variation in IPD incidence in the nine provinces, there was no statistically significant difference in provincial incidence when neonates were compared to non-neonates (data not shown).

The median age among neonates was six days (IQR 1.5 – 14) and among non-neonates was 231 days (IQR 127 – 386). There were more females among the neonates (151/286, 53%) than non-neonates (2,788/6,113, 46%) ($p = 0.02$) (Table 1, sex not documented in six neonates and 176 non-neonates). Of the 43 (43/92, 47%) neonates tested for HIV 44% (19/43) were HIV infected while 67% (1,218/1,831) of tested non-neonates (1,831/2,655, 69%) were HIV infected ($p < 0.01$) (Table 1). This difference was mainly because of a smaller proportion of EOD cases being HIV positive (4/16, 25%) than LOD cases (15/27, 56%; $p = 0.1$).
Clinical features and case-fatality ratios (CFR)

Clinical syndromes were available from 91/92 neonates and 2647/2655 non-neonates from ES sites only. Neonates presented most frequently with meningitis (36/91; 40%) compared to non-neonates (898/2647; 34%, \( p = 0.3 \)) (Table 1). Non-neonates presented most frequently with lower respiratory tract infections (1318/2647; 50%) compared to neonates (28/91; 31%, \( p < 0.01 \)).

The outcomes were available for 90/92 neonates and 2627/2655 non-neonates from the ES sites. The neonatal CFR was 31% (28/90), while the non-neonatal CFR was 26% (676/2627) (\( p = 0.13 \)) (Table 1). Cases with meningitis had the highest CFR among both neonates (39%; 14/36) and non-neonates (37%; 327/882) (Table 2).

Serotype distribution

Viable isolates were available for 76% (5021/6583) of reported cases, 195 neonatal and 4826 non-neonatal isolates. There were 16 isolates that were non-typeable, 1 neonatal and 15 non-neonatal. PCV7 serotypes were responsible for 31% (61/194) neonatal IPD and 59% (2853/4811) non-neonatal IPD (\( p < 0.05 \)) (Table 1). The PCV13 serotypes were responsible for 69% (134/194) of IPD in neonates and 84% in non-neonates (4042/4811) (Table 1). The proportion of PCV7 and PCV13 serotypes responsible for IPD in neonates was significantly lower than in non-neonates (\( p < 0.01 \)) (Table 1).

Forty-six percent (90/194) of neonatal IPD were accounted for by serotypes 5 (\( n = 18 \)), 1 (\( n = 17 \)), 19F (\( n = 15 \)), 3 (\( n = 14 \)), 8 (\( n = 13 \)) and 14 (\( n = 13 \)). These serotypes were responsible for 33% (1 572/4 811) of non-neonatal IPD serotypes (\( p < 0.01 \)) (Figure 2). Serotypes 1, 3 and 5 were more frequently isolated among neonates, 25% (49/194), than among non-neonates, 5% (247/4 811) (\( p < 0.01 \)) (Figure 2). The most common non-

neonatal serotypes were 14 (n = 805), 6B (n = 618), 6A (n = 580), 23F (n = 542), 19F (n = 520) (Figure 2). The non-PCV13 serotypes 8, 12F and 13 accounted for 13% (25/194) of neonatal and 4% (183/4811) of non-neonatal isolates (Figure 2).

**Antimicrobial susceptibility**

Antimicrobial susceptibility testing was performed on all 5021 viable isolates. Among neonates 76% (148/195) of isolates were susceptible to penicillin, compared to 50% (2424/4826) non-neonatal IPD isolates (p<0.01) (Table 1). Most isolates in this study were susceptible to ceftriaxone, 99% (194/195) and 98% (4757/4826) among neonates and non-neonates, respectively (Table 1). Cotrimoxazole non-susceptibility was lower among neonates (77/195, 39%) than non-neonates (3542/4826, 73%) (p <0.01) (Table 1). Among all tested isolates, 27% (1361/5021) were MDR, of which 15% (30/195) were neonatal and 28% (1331/4826) non-neonatal isolates (p <0.01) (Table 1).

Six serotypes most commonly associated with non-susceptibility to penicillin were serotypes 14, 19F, 6B, 23F, 6A and 19A. These accounted for 89% (42/47) and 91% (2124/2402) of penicillin non-susceptible isolates among neonates and non-neonates, respectively (Figure 3). These six serotypes were also the most frequent among the MDR isolates. Serotype 14 was the predominant MDR serotype: 40% (12/30) and 51% (684/1331) in neonates and non-neonates, respectively (Figure 3).

**Early-onset vs. late-onset disease**

Fifty-one percent (149/294) of neonates presented with EOD (Table 3). The median age for EOD was 0 days (IQR 0 – 2), with 66% (99/149) presenting within 48 hours of birth. The median age for LOD was 14 days (IQR 10 - 22). The EOD patients were more likely to have blood specimen sources than LOD patients (110/149, 74% vs. 24
LOD cases presented with meningitis more frequently than EOD cases (LOD: 25/48; 52% vs EOD: 11/43; 26%. \( p = 0.01 \)) (Table 3). The CFR was high in EOD and LOD, (14/44, 32% and 14/48, 29%, respectively).

Pneumonia in EOD (6/14, 43%) was associated with a higher CFR than in LOD, (1/14, 7%) \( (p < 0.03) \), while meningitis contributed substantially to the high CFR in both groups, (4/11, 36% in EOD; 10/25, 40% in LOD) \( (p = 0.7) \) (Table 4).
Discussion

In this study, conducted prior to introduction of PCV7 vaccination in South Africa, neonatal IPD accounted for an estimated 4.5% of IPD cases in children ≤ 2 years of age. Almost 50% of these neonates presented within the first week of life, with meningitis and bacteremia without focus, being the predominant clinical presentations. PCV13 serotypes contributed to 69% of all neonatal cases. The most frequent neonatal serotypes 1, 3 and 5 accounted for 25% of neonatal and only 5% of non-neonatal IPD cases. Neonatal IPD was associated with a high CFR (31%).

The national incidence of neonatal IPD, 5 per 100 000 live births in South Africa in 2008, was lower than the estimated global incidence of 36 per 100 000 live births in 2010 [4]. Billings et al reported an incidence of 16 per 100 000 live births, prior to the introduction of PCV, in less-developed United Nations (UN) strata countries [4]. Our incidence is also much lower than the incidence reported in Chile, of 59 per 100 000 population, and closer to that reported in the USA in 2006 (11 per 100 000 live births), and in England and Wales in 2013 (13 per 100 000 live births) prior to PCV, among <90 day old infants [5, 6, 7]. The incidence in this study is similar to that reported by Cutland et al, from a South African city, Soweto, where the incidence of neonatal sepsis due to the pneumococcus was reported as 8 per 100 000 live births among neonates [25]. In the Sowetan study S. pneumoniae was noted to occur less frequently than other common causes of neonatal sepsis, such as Streptococcus agalactiae, Staphylococcus aureus, Streptococcus viridans and Escherichia coli [25]. Differences in incidence may be attributed to the higher threshold for taking blood culture specimens in neonatal units in South Africa, variation in surveillance methodologies and completeness in reporting [4, 7]. The incidence we report may be an underestimate of true neonatal incidence as
infants with clinically evident, but microbiologically negative, sepsis would not have
been included in this study. In addition, the sensitivity of cultures among neonates is
low, attributable to inadequate sample volumes being submitted, as well as empiric
antimicrobials being commenced prior to cultures being taken [26, 27].

Among South African neonates, a large proportion of IPD cases, 51%, presented with
early-onset disease (EOD), similar to high-income countries like the USA and UK where 70% (19/27) and
77% (101/131), respectively, of neonatal IPD cases had EOD [5, 6]. This contrasts with
studies from Utah and Mexico, where only 11% (2/9) and 20% (25/126) of neonatal
cases, respectively, were EOD [28, 29]. The higher rates of EOD in South African
neonates and those of the USA and England and Wales may be due to similar at risk
populations, access to care and specimen-taking practices [4]. The variation between
and within countries may be attributed to differences in small hospital-based studies,
socioeconomic status, access to antenatal care and maternal and infant risk factors [28,
29].

In this study, 66% (99/149) of the EOD neonates presented within the first 48 hours of
life, similar to that reported by Ladhani et al in the UK, 67% (84/101), who indicated
that these infants were more likely to be premature [7]. Early-onset sepsis has been
found to be associated with prematurity, maternal chorioamnionitis, or social factors
influencing prenatal care [30]. We were unable to analyse for prematurity or other
maternal factors as these data were not collected during the study period.

Although the association of IPD and HIV infection in children has been well
documented in South African children [31], this was not clear among neonates in this
study. The high rates among neonates with IPD, 44%, may be because children that
were most ill or had signs of HIV were preferentially tested, or would have presented to a healthcare setting. In addition, HIV status data was only available for 15% (43/294) of neonates as there was no policy for universal HIV testing at birth at the time of this study. While the lower HIV positivity rate among the EOD cases was responsible for the significantly lower HIV positivity rate among neonates, compared to non-neonates, this observation cannot be explored further as the numbers tested were very low.

We observed a female sex preponderance in this study. Two studies, in Mexico and Denmark, reported a male sex preponderance [29, 32], while others do not report a sex preponderance [4, 5] among neonates with IPD. A male sex predisposition to neonatal sepsis, particularly Gram-negative sepsis, has been attributed to x-linked immunoregulatory genes [33, 34]. This predisposition may be specific to Gram-negative sepsis in neonates and therefore not consistently observed in neonatal IPD.

The predominant clinical presentation of neonates, bacteremia (42%) among EOD cases, and meningitis (52%) among LOD cases, in the South African setting was consistent with findings from England and Wales, and Mexico [7, 29]. Ladhani et al and Soto-Noguerón A et al reported bacteremia as the predominant presentation in the EOD cases and meningitis in the LOD cases [7, 29]. The more frequent diagnosis of bacteremia, and blood specimens in this study, among EOD cases may relate to an inability of the immature immune system in these very young babies to localize the infection [30, 35].

Although the CFR among neonates (31%) was higher than that among non-neonates (26%), this did not reach statistical significance. The neonatal CFR was also lower than those in other studies in England and Wales and the USA [7, 12]. This may be
attributed to an underestimation of the neonatal CFR, as infants who demised at home
would not have been included in this database. In addition, only 32% (90/294) of
neonates with IPD had outcomes available for analysis. Meningitis, an established risk
factor for death in patients with IPD [7, 36], was associated with the highest CFR
among both neonates and non-neonates in this South African context. The CFR in
neonates with IPD in this study was higher than that of neonates with sepsis due to more
frequently encountered pathogens, such as Group B Streptococcus, 16.9% [25] or
Escherichia coli, 6% [37], in South Africa.

In this study the neonatal isolates were generally more susceptible to antimicrobials
tested (penicillin and ceftriaxone) than the non-neonatal isolates, as in the USA and
Mexico, prior to PCV7 [12, 29]. This is not unexpected as the neonatal serotypes,
unlike the pediatric serotypes, are usually not associated with antimicrobial resistance
[14, 38, 39].

Our findings of 31% PCV7 serotypes in neonatal IPD are consistent with pneumococcal
vaccine studies from Mexico (34%), and England and Wales (44%), prior to PCV7 [29,
7]. The PCV13 serotype coverage among neonatal IPD isolates (69%) was also
comparable to those in Mexico (64%), and England and Wales (67%) [29, 7]. While
69% of neonatal IPD were due to PCV13 serotypes, this was significantly less than that
observed in the non-neonatal IPD group (84%). The common neonatal IPD serotypes 1,
3 and 5 among South African neonates is consistent with other studies from the USA
and Denmark [12, 32]. These serotypes have been reported to occur more frequently
among adults than children in the UK, Denmark, and South Africa [7, 32, 31]. This
supports the widely accepted premise of neonatal IPD being acquired via horizontal
spread from mother or adult caregiver [9].
Herd protection has been reported to play a role in decreasing the incidence of IPD in infants too young to be immunized, in studies post-PCV7 in England and Wales, USA and in South Africa [6, 7, 40]. However, no change was observed in PCV7 IPD in Mexico, in infants < 60 days old, after the introduction of PCV7, suggesting that herd protection did not extend to the mothers of these infants [29]. The option of maternal vaccination in such a setting, although reported to be safe, is currently not recommended due to insufficient evidence that it will provide neonatal protection [16, 17].

This study has several limitations. First, the data were collected using a laboratory-based surveillance system, where isolate submission is dependent on diligent local laboratory and surveillance staff. Case ascertainment also suffers from differential access to care and specimen-taking practices throughout the country. Only cases with known ages were included. In addition, audits performed on the surveillance database did not include private sector cases. Therefore, our estimates are an underestimation of actual disease burden in children ≤ 2 years old in South Africa. Second, as the study was performed retrospectively we were unable to check for maternal factors, such as premature labor, preterm rupture of membranes, maternal HIV infection, vaginal colonization or maternal IPD. Neonatal data, especially relating to HIV infection and outcomes, were also incomplete in our database. Third, susceptibility tests results were interpreted using meningitis breakpoints irrespective of the clinical syndrome, therefore the resistance rates appear higher in this study. This was appropriate as our study looked at trends over time, and not treatment outcomes. Fourth, susceptibility testing for ceftriaxone was revised from an agar dilution method to a CLSI-recommended broth.

microdilution method, using TREK panels, in 2009 [22], as the agar dilution method
was found to underestimate beta-lactam resistance [41].

Since 2014, there has been renewed global interest in neonatal mortality, the primary
cause of which is neonatal sepsis [42]. The highest mortality rates have been reported
in sub-Saharan Africa [42]. In this setting, this study is well-timed in describing IPD in
this vulnerable group.

Our findings suggest that the pneumococcus, while not as common a cause of neonatal
sepsis as other agents like Group B Streptococcus or E.coli, is associated with a higher
CFR. Neonatal IPD in this country is found to be similar to neonatal IPD in other
countries in terms of clinical presentation, serotype distribution, antimicrobial
susceptibility, and CFRs. The findings in this study establish a baseline against which
to interpret changes that may occur in neonatal IPD since the implementation of PCV in
South Africa.
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2016

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Figures and Tables for manuscript

Table 1: Characteristics of invasive pneumococcal disease in children ≤ 2 years of age in South Africa, 2003 – 2008, by age group (neonates vs non-neonates)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 28 days</td>
<td>≥28 days</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=294</td>
<td>N=6289</td>
<td>N=6583</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>p value</td>
<td>n (%)</td>
</tr>
<tr>
<td>Sexa</td>
<td>Female</td>
<td>151 (53)</td>
<td>2788 (46)</td>
<td>0.02</td>
</tr>
<tr>
<td>Specimen</td>
<td>Cerebrospinal fluid</td>
<td>106 (36)</td>
<td>2178 (35)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>186 (63)</td>
<td>3957 (63)</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2 (1)</td>
<td>154 (2)</td>
<td></td>
</tr>
<tr>
<td>Enhanced surveillance sites (ES)b</td>
<td>Yes</td>
<td>92 (31)</td>
<td>2655 (42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV statusc</td>
<td>Positive</td>
<td>19 (44)</td>
<td>1218 (67)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>24 (56)</td>
<td>613 (33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tested</td>
<td>43 (47)</td>
<td>1831 (69)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Clinical presentationd</td>
<td>Meningitis</td>
<td>36 (40)</td>
<td>898 (34)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>28 (31)</td>
<td>1318 (50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Bacteremia</td>
<td>27 (30)</td>
<td>185 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Othere</td>
<td>0</td>
<td>246 (9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age group</th>
<th>N=294</th>
<th>N=6289</th>
<th>N=6583</th>
<th>N (%)</th>
<th>p value</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial susceptibility</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Penicillin NS</td>
<td>47 (24)</td>
<td>2405 (50)</td>
<td>2449 (49)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone NS</td>
<td>1 (1)</td>
<td>69 (1)</td>
<td>70 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cotrimoxazole NS</td>
<td>77 (39)</td>
<td>3542 (73)</td>
<td>3619 (72)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multidrug-resistance</strong></td>
<td>Yes</td>
<td>30 (15)</td>
<td>1331 (28)</td>
<td>1361 (27)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCV serotypes</strong></td>
<td>PCV7</td>
<td>61 (31)</td>
<td>2835 (59)</td>
<td>2896 (58)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCV13</td>
<td>134 (69)</td>
<td>4042 (84)</td>
<td>4176 (84)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong>&lt;sup&gt;ª&lt;/sup&gt;</td>
<td>Demised</td>
<td>28 (31)</td>
<td>676 (26)</td>
<td>704 (26)</td>
<td></td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnotes: Abbreviations – HIV = Human immunodeficiency virus, NS = non-susceptible

<sup>†</sup>There were 5021 viable isolates with susceptibility data available, N = 195 neonates and N = 4826 non-neonates.

<sup>ª</sup>Outcomes were available for 90/92 neonates and 2627/2655 non-neonates (ES sites only).
Table 2: Case-fatality ratios (CFR) in children ≤ 2 years of age with invasive pneumococcal disease in South Africa, by age group (neonates vs. non-neonates) and clinical presentation, 2003 - 2008

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Age group</th>
<th>p-value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 28 days</td>
<td>≥28 days ≤2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFR (n/N)</td>
<td>CFR (n/N)</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>39 (14/36)</td>
<td>37 (327/882)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25 (7/28)</td>
<td>19 (245/1310)</td>
<td>0.4</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>17 (6/25)</td>
<td>21 (39/182)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Footnote: Abbreviations – CFR = case fatality ratio.

The clinical category of “other” (n = 246) was excluded from the analysis of case-fatality ratios by clinical syndrome, as there were no neonatal cases in this category. The cases without a clinical diagnosis, 1 neonate and 8 non-neonates, were excluded, as were the 2 neonates and 28 non-neonates whose outcomes were not available. Final denominators used: Neonates = 89; Non-neonates = 2374.

<table>
<thead>
<tr>
<th></th>
<th>Early-onset disease (0 – 6 days old)</th>
<th>Late-onset disease (≥7 &lt; 28 days old)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 149</td>
<td>N = 145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Sex^a</td>
<td>Female</td>
<td>73 (51)</td>
<td>78 (55)</td>
</tr>
<tr>
<td>Specimen</td>
<td>Cerebrospinal fluid</td>
<td>39 (26)</td>
<td>67 (46)</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>110 (74)</td>
<td>76 (52)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>ES sites</td>
<td>Yes</td>
<td>44 (48)</td>
<td>48 (52)</td>
</tr>
<tr>
<td>HIV status^b</td>
<td>Positive</td>
<td>4 (25)</td>
<td>15 (56)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>12 (75)</td>
<td>12 (44)</td>
</tr>
<tr>
<td></td>
<td>Tested</td>
<td>16 (36)</td>
<td>27 (56)</td>
</tr>
<tr>
<td>Clinical presentation^c</td>
<td>Meningitis</td>
<td>11 (26)</td>
<td>25 (52)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14 (33)</td>
<td>14 (29)</td>
</tr>
<tr>
<td></td>
<td>Bacteremia</td>
<td>18 (42)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Outcomes^d</td>
<td>Demised</td>
<td>14/42 (33)</td>
<td>14/48 (29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Early-onset disease (0 – 6 days old)</th>
<th>Late-onset disease (≥7 &lt; 28 days old)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>penicillin NS</td>
<td>24 (24)</td>
<td>23 (24)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Multidrug resistant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13 (13)</td>
<td>17 (18)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>PCV serotypes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV7</td>
<td>31 (31)</td>
<td>30 (32)</td>
<td>1.00</td>
</tr>
<tr>
<td>PCV13</td>
<td>63 (64)</td>
<td>71 (75)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Footnotes: Abbreviations – ES = enhanced surveillance sites, NS = non-susceptible, EOD = early-onset disease, LOD = late-onset disease, PCV = pneumococcal conjugate vaccine.

*Sex – there were 6 EOD and 2 LOD cases where the sex was unknown.  *b HIV status was not known in 28 EOD and 21 LOD cases from ES sites.  *c There were 91 neonates, 43 with EOD and 48 with LOD, with known clinical diagnoses.  *d Two cases from the ES sites did not have a documented outcome.  *e There was 1/195 viable isolates that was non-typeable among the LOD cases.

Table 4: Case-fatality ratios (CFR) in children < 28 days of age with invasive pneumococcal disease in South Africa, by age of presentation (early vs. late-onset disease) and clinical presentation, 2003 – 2008

<table>
<thead>
<tr>
<th></th>
<th>Early-onset disease</th>
<th>Late-onset disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 7 days</td>
<td>≥7 days – &lt; 28 days</td>
</tr>
<tr>
<td>Meningitis</td>
<td>36 (4/11)</td>
<td>40 (10/25)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>43 (6/14)</td>
<td>7 (1/14)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>19 (3/16)</td>
<td>33 (3/9)</td>
</tr>
</tbody>
</table>

Footnote: Abbreviations – EOD = early-onset disease, LOD = late-onset disease, CFR = case fatality ratio

Two of the 92 neonates from ES sites did not have an outcome documented. These 2, as well as the one neonate with an unknown clinical diagnosis, were excluded from the further analysis of CFR by clinical syndrome.
Figure 1: Incidence rates* (showing 95% confidence intervals) of invasive pneumococcal disease in neonates and non-neonates (“≥ 28 days - ≤ 2 years), by year, South Africa, 2003-2008 (n=6,583)

*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population
Figure 2: Most common serotypes among children ≤ 2 years of age, with invasive pneumococcal disease in South Africa: 2003 – 2008 by age group (neonates versus non-neonates) (* = PCV13 serotypes)
**Figure 3:** Serotype distribution of penicillin non-susceptible and multi-drug resistant (MDR) invasive pneumococcal disease isolates in children ≤ 2 years of age in South Africa, 2003 -2008, by age group

Footnote: Abbreviations: NS = non-susceptible; MDR = multi-drug resistant. These 7 serotypes accounted for 91% (43/47) of the penicillin non-susceptible neonatal isolates. Serotype 19F was the only serotype where the % neonatal penicillin non-susceptible isolates exceeded that of the non-neonates ($p = 0.03$). Serotype 14 was associated with the most multi-drug resistance among both neonates and non-neonates.
CHAPTER 3: REFERENCES

References for Literature review (Chapter 1)


Pneumococcal vaccination during pregnancy for preventing infant infection. The


CHAPTER 4: APPENDICES

1. Approval letters from post-graduate office (UKZN) and ethics committee (UKZN)
2. Valid ethics certificate
3. Case report form – NICD
1. Approval letters from post-graduate office (UKZN) and ethics committee (UKZN)
2 February 2010

Professor Y Coovadia  
Department of Medical Microbiology  
NRMSM  
UKZN  

Dear Professor Coovadia


The Postgraduate Education Committee ratified the approval of the abovementioned study on 2 February 2010.

Please note:

- The Postgraduate Education Committee must review any changes made to this study.

- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

[Signature]

Professor SR Thomson  
Dean’s Assistant: MMed Programme  
Postgraduate Education Committee

CC. Dr K Moodley  
Ms D Ramnarain  
Biomedical Research Ethics Committee  
Westville Campus

Postgraduate Education Administration,  
Medical School Campus

Postal Address: Private Bag 7, Congella, 4013, South Africa
Telephone: +27 (0)31 260 4327  
Facsimile: +27 (0)31 260 4401  
Email: postgrad@admin.ukzn.ac.za  
Website: www.ukzn.ac.za
27 August 2010

Dr. Krishnee Moodley
Department of Medical Microbiology, 4th Floor
Inkosi Albert Luthuli Central Hospital
800 Bellair Road,
Cato Manor
Durban


EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application dated 12 January 2010.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 12 July 2010 to queries raised on 01 March 2010 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 27 August 2010.

This approval is valid for one year from 27 August 2010. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

BREC is registered with the South African National Health Research Ethics Council (REC.290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee’s decision will be RATIFIED at a full sitting of the Biomedical Research Ethics Committee meeting to be held on 12 October 2010.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[Signature]

Professor D.R. Wassenaar
Chair: Biomedical Research Ethics Committee
2. Ethics certificate

Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that Krishnee Moodley successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 10/21/2014

Certification Number: 1592292
3. Case report form (CRF)

These were the forms utilized by the surveillance officers, from NICD, to collect additional data from patients presenting at one of the enhanced surveillance sites. The additional data included clinical diagnosis, outcomes, HIV status.

### GERMS-SA: National Laboratory-based Surveillance for Enteric, Respiratory and Meningeal Bacterial and Fungal Diseases in South Africa

**Protocol Version 1.4 (January 2009)**

**Clinical Case Report Form**

**National Microbiology Surveillance Unit (NMSU)**

**TEL: 011 386 6234 OR 011 555 0553 FAX: 011 386 6077**

### Surveillance Officer Name:

**Signature:**

<table>
<thead>
<tr>
<th>Sources of data:</th>
<th>Patient/Guardian</th>
<th>Clinician</th>
<th>Medical records</th>
<th>No record found</th>
<th>Refused participation</th>
</tr>
</thead>
</table>

| Lab Specimen No: | | Laboratory Name: |
|------------------| | |

<table>
<thead>
<tr>
<th>Hospital Name:</th>
<th>Hospital Number:</th>
<th>Ward:</th>
<th>Adult Ward</th>
<th>Paed Ward</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Gender:</th>
<th>F</th>
<th>Male</th>
<th>Black</th>
<th>Coloured</th>
<th>White</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Race:</th>
<th>Asian</th>
<th>Black</th>
<th>Coloured</th>
<th>White</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of Birth:</th>
<th>Day</th>
<th>Month</th>
<th>Year</th>
<th>Age Unclassified</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Surname:</th>
<th>Patient First Name:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Address:</th>
<th>Town/City:</th>
<th>Province:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Tel no: (H)</th>
<th>(W)</th>
<th>(C)</th>
<th>(Neighbour)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Has patient stayed in SA for the last month:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| If no, which country has patient come from: | |
|---------------------------------------------| |

| ID No: | ARV No: | |
|--------|---------| |

<table>
<thead>
<tr>
<th>Was patient referred from a hospital or chronic-care facility:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| If yes, specify: | |
|------------------| |

| Date of admission to acute hospital: | |
|--------------------------------------| |

<table>
<thead>
<tr>
<th>Was patient transferred to a step-down hospital:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| Date of transfer: | |
|-------------------| |

| If yes, name of step-down hospital: | |
|-------------------------------------| |

<table>
<thead>
<tr>
<th>Final outcome of patient:</th>
<th>Discharged</th>
<th>Died</th>
<th>RHTI</th>
<th>Absconded</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| Outcome date: | |
|---------------| |

<table>
<thead>
<tr>
<th>If discharged, patient discharged to:</th>
<th>Home</th>
<th>TB Hosp/Chronic Care Facility</th>
<th>Other</th>
<th>Specify:</th>
</tr>
</thead>
</table>

| Unclassified | |
|--------------| |

### Discharge Diagnosis:

<table>
<thead>
<tr>
<th>Meningitis</th>
<th>LRTI</th>
<th>Dysentery</th>
<th>Diarrhoea</th>
<th>Fungo/aemia/Bacteriaemia without focus</th>
<th>Other</th>
<th>Specify:</th>
</tr>
</thead>
</table>

| Cryptococcus sp. | Date of specimen collection: | |
|------------------|-------------------------------| |

<table>
<thead>
<tr>
<th>Haemophilus sp.</th>
<th>N. meningitidis</th>
<th>Shigella sp.</th>
<th>Site of specimen collection:</th>
<th>CSF</th>
<th>Blood</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>S. pneumoniae</th>
<th>P. jiroveci</th>
<th>Salmonella sp.</th>
<th>Joint Fluid</th>
<th>Other</th>
<th>Specify:</th>
</tr>
</thead>
</table>

### Severity of Illness (on the day the positive specimen was taken):

<table>
<thead>
<tr>
<th>Temp:</th>
<th>°C</th>
<th>Unclassifed</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>BP:</th>
<th>/</th>
<th>Unclassifed</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Mechanical Ventilation:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cardiac Arrest:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>GCS:</th>
<th>15</th>
<th>Unclassifed</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Mental Status:</th>
<th>Alert</th>
<th>Disorientated</th>
<th>Stuporous</th>
<th>Comatose</th>
<th>Unclassifed</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Previous admissions in the last 12 months:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| Number of admissions: | |
|-----------------------| |

### Cotrimoxazole Prophylaxis (not current treatment) :

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| Dosage: | |
|---------| |

<table>
<thead>
<tr>
<th>Date Unk:</th>
<th>Date initiated:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Compliant in last month:</th>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

### TB Treatment (from the last 3 months and current):

<table>
<thead>
<tr>
<th>TB Treatment:</th>
<th>Drugs:</th>
<th>Date initiated:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

| Date stopped: | |
|---------------| |

**GERMS-SA: National Laboratory-based Surveillance for Enteric, Respiratory and Meningeal Bacterial and Fungal Diseases in South Africa**

**Protocol Version 1.4 (January 2009)**

**Clinical Case Report Form**

**National Microbiology Surveillance Unit (NMSU)**

TEL: 011 396 6334 OR 011 555 0533  FAX: 011 396 6077

---

### Laboratory Specimen Number:

**Immunocompromising conditions:**

- Alcohol dependency
- Chronic renal failure
- Heart failure
- Kwashiorkor
- Marasmus
- Nephrotic syndrome
- Malignancy
-Specify:
- History of head injury/head surgery
- Hydrocephalus with VP shunt
- Sickle cell anemia
- Organ transplant
- Specify:
- Burns
- Coronary Artery Disease
- Diabetes mellitus
- Immunoglobulin deficiency
- Splenectomy/ asplenia
- Other
- Specify:
- Cirrhosis/ liver failure
- Emphysema/COPO
- Immunosuppressive Rx (steroid/chemo)
- Systemic Lupus
- None
- Specify:
- Erythematous (SLE)

**HIV status prior to this admission:**

- Pos
- Neg
- Unk

- HIV related counseling offered by SC: Yes  No

**HIV status at this admission:**

- Pos
- Neg
- Unk

- HIV test performed by SO: Yes  No

**For children <18 months: HIV PCR Done:**

- Yes
- No
- Unk

**Was the child exposed to HIV?**

- Yes
- No
- Unk

**If HIV unknown, why was patient not tested:**

- Patient died
- Patient not seen
- No guardian
- Patient confused/comatose

- P/H referred for VCT elsewhere
  - Reason for refusal: Unk

**Clinical markers of HIV:**

- Diarrhoea >1/day
- Oral candidiasis
- Suspected PJP
- None

- Kaposis sarcoma
- Tuberculosis
- HIV wasting
- Unk

**CD4 count closest to specimen collection date:**

- Absolute: Unk
- Percentage: % Unk
- Date taken: Unk

**Viral load closest to specimen collection date:**

- <400
- 400-10,000
- >10,000
- Unk
- Date taken: Unk

**Any antiretroviral use:**

- Yes
- No
- Unk

- If yes: Current
- Previous
- Perinatal

**If HIV positive and no current ARV use, has the patient been referred to an ARV clinic:**

- Yes
- No
- Died
- Unk

---

**PLEASE COMPLETE RELEVANT SECTIONS FOR SPECIFIED ORGANISMS**

**Haemophilus spp., S. pneumoniae, N. meningitidis, Salmonella spp., Shigella spp. ONLY**

- Number of children, <18 years, living with patient: None
- Place of safety: Unk

**Antibiotic use prior to this specimen collection date:**

- ABX in 24hr before specimen: Yes
- No
- Unk
- Date initiated: Unk

**Name of antibiotic:**

1.  2.  3.  4.

**Other ABX in last 2 months:**

- Yes
- No
- Unk
- In last 30 days: Yes  No  Unk

**Name of antibiotic:**

1.  2.

**Antibiotic use in hospital during this admission (excluding TB therapy):**

- Weight: 1-10 kg
  - Antimicrobial therapy unknown
  - Antimicrobial therapy not prescribed

**Name of antimicrobial**

- Dose
- Route
- Date initiated
- Total doses given/no. of days

1.  2.  3.  4.  5.

---

Page 2 of 5

January 2009

63 of 71

GERMS-SA: National Laboratory-based Surveillance for Enteric, Respiratory and Meningeal Bacterial and Fungal Diseases in South Africa
Protocol Version 1.4 (January 2009)
Clinical Case Report Form
National Microbiology Surveillance Unit (NMSUJ)
TEL: 011 266 6234 OR 011 555 0353 FAX: 011 266 6077

<table>
<thead>
<tr>
<th>Laboratory Specimen Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus spp. and S. pneumoniae ONLY</td>
</tr>
<tr>
<td>Vaccination status for <em>Haemophilus influenzae</em>:</td>
</tr>
<tr>
<td>If &lt;15 years old, did patient receive <em>Haemophilus influenzae</em> type b (HiB) vaccine?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>5 weeks</td>
</tr>
<tr>
<td>10 weeks</td>
</tr>
<tr>
<td>14 weeks</td>
</tr>
<tr>
<td>18 month booster (Pentacel)</td>
</tr>
<tr>
<td>Catch up/ Other</td>
</tr>
<tr>
<td>Catch up/ Other</td>
</tr>
<tr>
<td>Catch up/ Other</td>
</tr>
<tr>
<td>Source of vaccine status information:</td>
</tr>
<tr>
<td>Directly from clinic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cryptococcus spp. ONLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal prior to this admission:</td>
</tr>
<tr>
<td>Fluconazole</td>
</tr>
<tr>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Is this the first episode of cryptococcosis?</td>
</tr>
</tbody>
</table>

Management during this admission:

<table>
<thead>
<tr>
<th>Antifungal therapy unknown</th>
<th>Antifungal therapy not prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Frequency</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Daily</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Daily</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>On discharge, was patient given fluconazole?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumocystis jirovecii ONLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP treatment during this admission:</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
</tr>
<tr>
<td>Etoposide</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>PCP therapy unknown</td>
</tr>
<tr>
<td>PCP therapy not prescribed</td>
</tr>
<tr>
<td>On discharge was patient given cotrimoxazole?</td>
</tr>
</tbody>
</table>

64 of 71 January 2009