

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

Bacterial Meningitis in neonates and children in South Africa

Student: Karla Mari Thomas (THMKAR005)

**SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In fulfilment of the requirements for the degree**

Master of Medicine (MMed) Paediatrics

**Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN**

Date of submission: February 2013

Supervisor: Prof M Levin

School of Adolescent and Child Health, University of Cape Town

DECLARATION

I, *Karla Mari Thomas* hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Date:

University of Cape Town

Contents

- 1. Section A: Protocol**
- 2. Section B: Literature review**
- 3. Section C: Manuscript**
- 4. Section D: Appendices**
 - **Ethics Approval**
 - **Ethics Renewal**
 - **CDW cover letter**
 - **CDW request form**
 - **Instructions to authors: The International Journal of epidemiology**
 - **Acknowledgements**

Bacterial meningitis in neonates and children in South Africa

A: Introduction

1. The problem:

Acute bacterial meningitis is an important cause of morbidity and mortality in newborns and children^{i, ii, iii}. In South Africa fatality rates among infants and children due to meningitis varies between 3 to 7 percentⁱⁱⁱ.

Acute bacterial meningitis is defined as the inflammation of the meninges. It is caused by various bacteria and the specific aetiology is age dependant^{iv}. In the neonatal period the causative organisms are: Group B streptococci, Gram - negative bacilli (e.g.: *E. coli*, *Klebsiella spp*, *Enterobacter spp*, *Salmonella spp*) and *Listeria monocytogenes*^{iv, v}. In infants and children up to the age of 5 the most common causative organisms include: *Streptococcus pneumoniae*, *Haemophilus influenzae type B* (Hib) and *Neisseria meningitidis*^{iv, v}. The two chief causes of bacterial meningitis in children older than 5 are *S. pneumoniae* and *N. meningitidis*^{iv, v}.

Various studies have been performed to look at the profile of meningitis among the paediatric population^{i, vi, ii}.

A study looking at bacterial meningitis among Cape metro pole children from 1991 to 1992 found that *N. Meningitidis* was the most common causative organism of bacterial meningitis in this study's setting^{vii}. This was followed by *H. influenzae* and *S. Pneumoniae* respectively^{vii}. The average age of children in this study with Haemophilus and Pneumococcal meningitis were similar at 9 and 7,5 months respectively. Those with *N. Meningitidis* meningitis were older at an

average of 22 months^{vii}. Two earlier studies conducted in the Western Cape also found that *N. Meningitidis* was the most common causative organism of childhood meningitis in the Western Cape^{viii, ix}. A 2-year retrospective study of the epidemiology of bacterial meningitis was conducted in Johannesburg from 1980 – 1982^x. This study looked at the aetiology, age distribution, seasonal variation and antibiotic sensitivity patterns of the organisms causing bacterial meningitis^x. *N. Meningitidis* was the organism most frequently isolated, followed by *S. Pneumoniae*, *H Influenzae*, *E. Coli* and Group B streptococci^x. Certain seasonal trends were noted: Meningococcal and Pneumococcal meningitis occurred more frequently in spring and winter, while there was no seasonal peak for *Haemophilus meningitis*^x. Most of the cases of *Haemophilus meningitis* were among children under 3 years old^x. A surveillance of bacterial meningitis in Mozambique found that *H. influenzae b* was the most common causative organism of childhood bacterial meningitis. This was followed by *S. Pneumoniae* and *N. Meningitidis*^{xi}.

With the advent of preventative strategies, most notably the introduction of the *Haemophilus* type B vaccine and the pneumococcal conjugate vaccine, one would expect a changing pattern in the incidence of certain causative organismsⁱⁱ. A study documenting the causative organisms of bacterial meningitis in Korean children from 1996 – 2005 found that *Haemophilus influenza meningitis* had declined especially after 2001 when the *H. influenza b* vaccine was introducedⁱ. Similarly, a Greek study looking at the epidemiological patterns of acute bacterial

meningitis showed a reduction of Haemophilus b since the introduction of the H. influenza b vaccineⁱⁱ. In developed countries, the routine use of the Haemophilus B vaccine has shown a reduction of 99% of invasive Haemophilus disease^{iv}. The vaccine has also reduced the Haemophilus B disease in developing countries^{xii} South Africa was the first African country to finance the introduction of the Haemophilus b vaccine into the vaccination schedule from July 1999^{xii} There has been a significant decrease in the incidence of invasive Haemophilus b disease following the introduction of the Haemophilus b vaccine into the vaccination schedule^{xii}. The afore mentioned study in Mozambique concluded that more than 40% of the bacterial meningitis cases were potentially preventable by the Pneumococcal or Hib conjugate vaccines^{xi}.

S. pneumoniae is a very important cause of meningitis amongst children and infantsⁱ. The conjugate Pneumococcal vaccine covers against seven of the pneumococcus strainsⁱ. Since the introduction of this vaccine in the USA the incidence of *S. pneumoniae* meningitis has declined by 30.1 %ⁱ. Despite this, *S. pneumoniae* still remains the most common cause of bacterial meningitis in children in the USAⁱ. This is due to the emergence of pneumococcal strains not covered by the conjugate vaccineⁱ. The seven valent Pneumococcal conjugate vaccine was registered in South Africa in 2005 but only introduced as part of the public sector immunisation schedule in April 2009.^{xii} Children born after 15 February 2009 were eligible for the Pneumococcal conjugate vaccine and no catch up immunisation was planned^{xii}. The use of the Pneumococcal and H. Influenza b vaccines have also been associated with decreased incidence of Pneumococcal and

Haemophilus B meningitis in populations not immunised, through herd immunity^{xiii}.

A retrospective study done at Tygerberg Hospital in the Western Cape looked at the following aspects of neonatal meningitis: mortality, CSF and microbiological findings^{xiv}. This study looked at the records of those treated for bacterial meningitis from July 1981 to June 1992^{xiv}. Eighty eight patients were included. In this study the most common causative organism of neonatal meningitis was group B Streptococcus followed by *E. coli* and *K pneumoniae*.^{xiv} In this study there was only one case of *Listeria Monocytogenes*, showing that Listeria is a rare cause of neonatal meningitis in our setting^{xiv}.

Amongst neonates, group B streptococci remain an important cause of meningitis^{i,vi}. Intrapartum antibiotics (penicillin or ampicillin) administered to women colonised rectally or vaginally with group B streptococci has shown to reduce early onset neonatal group B streptococcal sepsis^v. Intrapartum antibiotic prophylaxis does not, however, significantly decrease the rate of late onset group B streptococcal sepsis and, unfortunately, most cases of group B streptococcal meningitis occur later in the neonatal period^v. Immunisation of mothers with the group B streptococcal conjugate vaccine may be used as a future strategy to prevent neonatal group b streptococcal meningitis^{iv}.

The Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS – SA) has published surveillance reports in the communicable

diseases surveillance bulletin (available on the National Institute for Communicable Diseases website.)

GERMS –SA found that the overall incidence of *N. Meningitidis* remained the same in 2008 and 2009^{xv}. Five percent of *N. Meningitidis* isolates were intermediately resistant to penicillin^{xv}. GERMS – SA still, therefore, recommends penicillin as the anti biotic of choice for confirmed meningococcal disease^{xv}. When looking at *H. Influenzae*, GERMS –SA found that serotype b was the most common *H. Influenzae* causing illness in infants^{xv}. In 2009 there was an increase in Hib disease in those under 1 year of age^{xv}. It was found that 19% of Hib were resistant to ampicillin^{xv}. The age group most at risk of contracting invasive pneumococcal disease was those under 1 years old^{xv}. GERMS – SA did, however, find that there has been a decrease in invasive Pneumococcal disease in infants under 1 year. They attributed this to the introduction of the conjugate Pneumococcal vaccine in South Africa in 2009^{xv}. The GERMS –SA data for 2009 showed an increase in Pneumococcal resistance to penicillin and ceftriaxone^{xv}. GERMS –SA, however, believes that this increase is due to a change in laboratory methods introduced in 2009^{xv}. It is therefore recommended that suspected Pneumococcal meningitis be treated empirically with ceftriaxone and vancomycin^{xv}.

2. Objective:

To investigate the aetiology of acute bacterial meningitis in South African newborns and children from 2005 - 2010.

- To determine the prevalence (and 95 % confidence interval) of causative organisms of acute bacterial meningitis among culture positive cerebral spinal fluid (CSF) in four paediatric periods namely: 1. The neonatal period (day 0 – 28 days of life); 2. 1 – 3 months; 3. 3 months to 5 years) and 4. Children older than 5 years of age up till 12 years.

3. Subsidiary Objectives:

- To compare the prevalence (and 95% confidence interval) of the causative organisms among culture positive CSF between the various age groups. (The null hypothesis being: There is no difference in the causative organisms between the 4 age groups)
- To determine the relative proportions (and 95% confidence interval) of pneumococcal meningitis prior to and after the introduction of the conjugate pneumococcal vaccine. (The null hypothesis being: There is no difference in the incidence of pneumococcal meningitis before and after the introduction of the conjugated pneumococcal vaccine.)
- To determine antibiotic resistance and sensitivity patterns among the organisms causing bacterial meningitis in neonates and children.

B Methods:

1. Study Design

This will be a retrospective descriptive and analytical cross sectional study.

2. Subject selection:

The subjects of this study will be patients in the paediatric population (age 0 – 12years) who have had a positive culture result on CSF from 2005 - 2010 in the provinces, whose data, is captured on the Corporate Data Warehouse (CDW). This includes all South African provinces except for Kwazulu Natal. The sample will represent the paediatric population who make use of the government hospitals in South Africa. The inclusion criteria will be the following: patients aged 0 – 12years; an organism was cultured on the subject's CSF. Exclusion criteria will be: meningitis which is not acute: i.e. mycobacterium tuberculosis, patients older than 12, no organism cultured on the subject's CSF.

3. Measurement:

Instruments:

Database:

A database will be created in excel onto which the various variables will be captured. The variables will be listed under the columns. Each row will represent a patient. The variables will be as follows:

A: Patient Number

B: Date of birth of patient

C: Date when specimen taken

D: Organism grown

E. Antibiotic name

F: Sensitivity

G: Province of origin

H: Hospital name

I: Ward from which sample was taken

The following information will be needed:

- A list of the positive CSF culture results.
- The organism cultured
- Date of birth of the patient
- Date when CSF specimen take
- The name of hospital (this won't be published)
- The ward from which the sample was taken
- Details of all antibiotic sensitivity testing(resistance and sensitivities)

The data will be obtained from the Corporate Data Warehouse (CDW). All National Health Laboratory Services' data (except for Kwazulu Natal) is captured on the CDW.

C. Analysis:

Descriptive analyses such as working out the frequency distribution of various causative organisms will be done in Excel. Statistical analyses will be performed using the following software: Stata and epicalc 2000. The prevalence of causative organisms per year and per age group will be calculated and depicted in bar graphs (error bars will depict the 95% confidence interval). Bar graphs for each year will be created and this will depict trends over time. The prevalence ratio will also be used to compare the causes of meningitis between the various age groups.

The relative proportions of pneumococcal meningitis prior to and after the introduction of the conjugate pneumococcal vaccine will be calculated and depicted on a bar graph. (The pneumovac vaccine was included in the South African vaccine schedule on 1 April 2009. Children born after 15 February 2009 were eligible for the pneumovac vaccine^{xii}. The assumption will be that patients born after 15 February 2009 were vaccinated with the conjugate pneumococcal vaccine.) This will also show the change of prevalence of pneumococcal meningitis over time. The antibiotic resistance and sensitivity patterns among the organisms causing bacterial meningitis in neonates and children will be calculated. Organisms will be looked at individually and the rate of resistance to the relevant antibiotics will be calculated.

The chi-squared test will be used to test the hypotheses. The level of significance will be 0.05 and a P value of less than 0.05 will be deemed as statistically significant.

D Ethics and Communication:

1. Ethics:

The data used will be unlinked; i.e. the names of the patients will not be part of the data set. The data will be obtained only after receiving consent from the Corporate Data Warehouse. This study does implement the ethical principals of justice, beneficence and non – malificience. The study will benefit the paediatric population of South Africa because it will give health care professionals an insight into the causes of meningitis and will help in future treatment and preventative strategies (justice). The study will pose no harm to paediatric patients. (non- malificience)

2. Reporting and implementation:

The results of this study will be fed back to the school of child and adolescent health at UCT. The study will be written up for an MMed and will be submitted for publication. The feedback will serve as a platform to inform colleagues about meningitis among the South African paediatric population. It may also open up new research questions and lead to more studies.

E. Logistics:

This study will not require many resources. The following resources will be required: Access to a computer, certain software packages and access to the internet. These resources are available at the UCT medical school library.

References:

-
- ⁱ Cho HK, Lee H, Kang JH, Kim KN, Kim DS, Kim YK, Kim JS, Kim JH, Kim CH, Kim HM, Park SE, Sung HO, Chung EH, Sung HC, Young YC, Hur JK, Young JH, Lee HJ, Kim KH. The Causative Organisms of Bacterial Meningitis in Korean Children in 1996 – 2005. *J Korean Med Sci* 2010; **25**: 895- 899.
- ⁱⁱ Theodoridou MN, Vasilopoulo VA, Atsali EE, Pangalis AM, Mostrou GJ, Syriopoulou VP, Hadjichristodoulou CS. Meningitis registry of hospitalised cases in children: epidemiological patterns of acute bacterial meningitis throughout a 32 year period. *BMC Infectious Diseases* 2007; **7**: 101
- ⁱⁱⁱ Coovadia HM, Wittenberg DF. Paediatrics and child health. A manual for health professionals in developing countries. Fifth edition. Cape Town. Oxford University Press 2003
- ^{iv} Chavez – Beuno S, McCracken GH Jr, Bacterial Meningitis in Children. *Pediatr Clin N Am* 2005; **52**: 795 – 810
- ^v Saez- Llorens X, McCracken GH Jr Bacterial meningitis in children. *Lancet* 2003; **361**: 2139 – 2148
- ^{vi} Holt DE, Halket S, de Louvois J, Harvey D. Neonatal meningitis in England and Wales: 10 years on. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**: F85- F89
- ^{vii} Hussey G, Schaaf H, Hanslo D, Hitchcock J, Coetzee G, Pitout J, Malan H, Donald P. Epidemiology of post – neonatal bacterial meningitis in Cape Town Children. *SAMJ* 1997 **87** (1): 51 - 56
- ^{viii} Potter P C, Donald P R, Moodie J, Slater C, Kibel M A. Meningitis in Cape Town children. *SAMJ* 1984 **66**: 759 – 762
- ^{ix} Donald P R, Burger P J, Becker W B. Paediatric meningitis in the western Cape. A 3 – year hospital – based prospective survey. *SAMJ* 1986 **70**: 391 - 395
- ^x Liebowitz L D, Koornhof H J , Barret M et al . Bacterial Meningitis in Johannesburg – 1980 –1982. *SAMJ* 1984 **66**: 677 - 679

^{xi} Roca A, Bassat Q, Morais S, et al. Surveillance of Acute Bacterial Meningitis among Children admitted to a district Hospital in Rural Mozambique. *Clin Infect Dis* 2009;**48**:S172-180

^{xii} Vonn Gottberg A. Bacterial Meningitis in the era of paediatric vaccination against the encapsulated pathogens. *CME* June 2010; **28**(6): 252 - 259

^{xiii} Kim K. Acute bacterial meningitis in infants and children. *Lancet Infect Dis* 2010; **10**: 32 - 42

^{xiv} Nel E. Neonatal Meningitis: Mortality, Cerebrospinal Fluid, and Microbiological Findings. *Journal of Tropical Pediatrics* 2000 August; **46**(4): 237 – 239

^{xv} Respiratory & Meningeal Pathogens Reference Unit, National Institute for Communicable Diseases. *Communicable Diseases Surveillance Bulletin* May 2010: 34 - 43

University of Cape Town

Bacterial Meningitis in neonates and children in South Africa: a literature review

Background:

Acute bacterial meningitis is an important cause of morbidity and mortality in newborns and children.¹ In South Africa the fatality rate among infants and children due to bacterial meningitis is between three to seven percent.²

Bacterial meningitis is defined as inflammation of the meninges.¹ A bacterial agent colonizes the nasopharynx and then invades the nasal mucosa. This is followed by bacteraemia and subsequent entry of bacteria into the cerebrospinal fluid and the meninges.³

Acute bacterial meningitis is caused by various bacteria and the specific aetiology is age dependant.⁴ The epidemiological pattern, as well as morbidity and mortality of bacterial meningitis is also dependant on geographical location.^{1,3} Developing countries have a higher mortality as well as a different epidemiological pattern as compared to developed countries.³ Review articles have documented the common causes of acute bacterial meningitis in various age groups. In the neonatal period the common causative organisms are: Group B Streptococci, Gram negative bacilli (e.g.: *E. coli*, *Klebsiella spp*, *Enterobacter spp*, *Salmonella spp*) and *Listeria monocytogenes*.^{4,5} The causative organisms in the age group 1 – 3 months are the same as the neonatal age group as well as *Streptococcus pneumoniae*, *Haemophilus influenzae Type B* (Hib) and *Neisseria meningitidis*.^{1,4,5} In infants and children aged 3 months to 5 years the most common causative organisms are: *S. pneumoniae*, Hib and *N. meningitidis*.^{1,4,5} The two chief causes of bacterial meningitis in children older than 5 years old are: *S. pneumoniae* and *N. meningitidis*.^{1,4,5}

Knowing the most common causes of bacterial meningitis in the various age groups helps health professionals to initiate the best possible empiric antibiotic therapy.^{1,4,5} Two recent

review articles recommended the following empirical antibiotic regimes for meningitis: age less than 1 month: ampicillin plus either gentamicin or cefotaxime; age 1 – 3 months: ampicillin plus either cefotaxime or ceftriaxone, (vancomycin can be added if pneumococcal meningitis is suspected); ages 3 months – 21 years: cefotaxime/ceftriaxone plus either vancomycin or rifampicin (in areas where there is a high incidence of resistant *S pneumoniae*).^{1, 6} The essential drug list for South African paediatrics recommends the following empiric treatment regimes: neonates: ampicillin plus either cefotaxime or ceftriaxone; children > 60 days: cefotaxime or ceftriaxone.⁷

With the advent of preventative strategies, especially new vaccines such as the Hib vaccine and the pneumococcal conjugate vaccine, one would expect a change in the incidence of certain causative organisms.¹ The Hib vaccine has caused a 99% reduction in Hib invasive disease in developed countries.⁴ The conjugate pneumococcal vaccine (pcv) has also been shown to have substantially reduced the incidence of pneumococcal meningitis in children younger than 5 years in many high – income countries.¹ It is important to note that in Africa the Hib and pcv have not been widely implemented.

Recent review articles on bacterial meningitis focus more on developed countries and there is less information on meningitis in developing countries. In this literature review, an emphasis has been made on meningitis in developing countries, especially African countries. It is also important to note that the conjugate pneumococcal vaccine was not available in Africa.

Objectives:

This literature review on the aetiological agents of bacterial meningitis among neonates and children aims to:

- identify the common causative organisms of acute bacterial meningitis in neonates and children in both developed and developing nations;
- review the impact of the Hib and pneumococcal vaccines on haemophilus and pneumococcus meningitis;
- review the antibiotic sensitivity patterns of the common causative organisms of bacterial meningitis.

Search Strategy:

The literature review search was conducted on PubMed (www.ncbi.nlm.nih.gov/pubmed)

Two search strings were used: 1. Acute bacterial meningitis in children and newborns.

PubMed searched using the following search strategy: “Acute AND (meningitis, bacterial)

OR (meningitis) AND (bacterial) OR (bacterial meningitis) OR (bacterial) AND (meningitis) AND (infant, newborn) OR (infant) AND (newborn) OR (newborn infant) OR (newborns) AND (child) OR (child) OR (children)

2. Acute bacterial meningitis in newborns and children in South Africa.

The inclusion criteria were: English language articles; articles focusing on bacterial meningitis in newborns/ neonates and children (newborns/neonates were defined as age less than or equal to 28 days; children were defined as age less than 18 years). Articles that did not exclusively focus on meningitis and or children and newborns, but those which did include the above subjects were also included in this literature review.

The main criteria for inclusion was studies looking at the various aetiological causes of acute bacterial meningitis among children and newborns/neonates but those articles focusing on at least three aetiological causes were also included.

Exclusion criteria were as follows: articles focusing solely on adults (defined as older than 18 years old); articles focusing on only one bacteriological cause of meningitis, articles that reported only on diagnostic procedures or only on sequelae of meningitis, articles on meningitis not caused by bacteria and articles published in languages other than English. Abstracts derived from the above mentioned PubMed search were reviewed. Those abstracts that had any exclusion criteria were excluded. Those with inclusion criteria were reviewed in full text. Those articles reviewed in full text were further filtered. Those that met the inclusion criteria stated above but did not separate out the meningitis data or where the meningitis data represented a very small number of the total number of subjects studied were also excluded. Those studies which had patient cohorts already included in other more comprehensive studies were excluded.

Reference lists of fully reviewed articles were also screened for other articles to include in this literature review. Articles obtained from colleagues (i.e. project supervisor and scientific review panel) were also reviewed and if they met the inclusion criteria they were included in the literature review.

Results:

The PubMed search was first conducted on 5 January 2011. (The same search was repeated on 20 June 2011 at the time of writing the literature review so as to ensure that the literature review was as current as possible. This was again repeated on 17 January 2013 just prior to submission.) The two search strings yielded 257 articles. Those abstracts as well as those obtained from colleagues were reviewed. The inclusion and exclusion criteria as defined in the above 'Search Strategy' section were applied and 33 articles were reviewed in full text. Twenty articles were included in this literature review. Twelve studies were from developing countries (1 from Asia, 6 from South Africa, 6 from African countries excluding South

Africa). Seven studies were from developed nations (1 from Asia, 3 from Europe and 3 from the United States of America).

The data was collected from 1974 – 2009. One study included children and adults as the subjects, 2 studies focused only on neonates, 5 studies looked at children only, 9 studies focused on neonates and children while 3 studies looked at bacterial meningitis in neonates, children and adults. Seventeen articles looked at all the aetiological agents responsible for bacterial meningitis in their study populations. The three studies conducted in the United States of America (USA) only looked at three (*S. pneumoniae*, *H. influenzae* and *N. meningitidis*)⁸ or five aetiological agents (*H. influenzae*, *S. pneumoniae*, *N. meningitidis*, *L. monocytogenes* and group B streptococcus).^{9, 10} Nineteen studies' main objective was to look at the causative organisms of meningitis. Of these studies only two looked at bacterial as well as viral aetiologies.^{11,12} One study mainly looked at how to diagnose bacterial meningitis but it did include the causative organisms of bacterial meningitis in its results.¹³

South Africa

As stated before there were six articles from South Africa. One article only looked at meningitis exclusively in neonates¹⁴. Not one of the South African articles looked at subjects from more than one South African province. Five studies^{11,12,14 15, 16} were conducted in the Western Cape and one study was conducted in Gauteng¹⁷. The study exclusively looking at neonatal meningitis was conducted at a tertiary care hospital in the Western Cape.¹⁴ It was a retrospective study and the data derived was from an 11 year period. The most common causative organism identified was group B streptococci. This was followed by *E. coli* and *K. pneumoniae*. If one looked at the gram negative bacilli as a whole group, then this group was responsible for the most cases of neonatal meningitis. The incidence of neonatal meningitis was 0.72/ 1000 live births.¹⁴

N. meningitidis was the most common cause of bacterial meningitis four of the South African studies looking at bacterial meningitis in children.^{11,12,15,17} The most recent study found that the commonest non mycobacterium cause of childhood bacterial meningitis was *S. pneumoniae*.¹⁶ In the Johannesburg study, almost all of the *H. influenzae* cases occurred in children 1 month – 3 years old.¹⁷ Two of these studies reported on neonatal meningitis separately.^{12,17} Gram negative bacilli and group B streptococci were the predominant organisms in neonatal meningitis.^{12,17}

Three studies reported on antibiotic sensitivity patterns. *H. Influenzae* was found to be resistant to ampicillin in 2/34 (6%) of cases in one study¹² while none of the *H. influenzae* isolates were resistant to chloramphenicol in another study.¹⁷ Of the *N. meningitidis* isolates 24/ 114 (21%) were resistant to sulphonamides in one study¹² while 6/18 (33%) were resistant in another.¹¹ 8/17(47%) of *S. pneumoniae* isolates were resistant to penicillin in the Johannesburg study¹⁷, while none of the 28 *S. pneumoniae* isolates in a Western Cape study were resistant to penicillin.¹²

Only one of these studies was conducted in the era of the Hib vaccine¹⁶ and none were conducted in the era of the pneumococcal conjugate vaccine.

Other developing countries

Six African studies were included in this literature review. Three studies were conducted in rural areas^{18,19,20} while three studies were based in urban centres.^{21,22,23} In the neonates the most common causative organisms were Group B Streptococci and gram negative bacilli in two studies^{18,23}, while one study found that *S.pneumoniae* was the commonest causative organism of neonatal meningitis followed by *E. Coli* (gram negative bacilli).²¹ *S. pneumoniae* and *H.influenzae* were the main causative organisms in infants and children in all the African studies looked at in this literature review.¹⁸⁻²³ Four of the studies found that the sensitivity of *S.pneumoniae* to penicillin was relatively high (> 81%)^{19,20,22,23} Of the

S.pneumoniae isolates tested in a Kenyan study 26% were resistant to penicillin¹⁸. Three studies found relatively high resistance to ampicillin and chloramphenicol among *H. influenzae* isolates (> 20%).^{18,22,23} The two studies which reported on *N. meningitidis* sensitivity stated that all isolates were sensitive to penicillin and chloramphenicol.^{20,22} None of these studies were conducted in the era of the conjugate pneumococcal vaccine or Hib vaccine.^{18 - 23}

The only other study from a developing nation included in this literature review was from India.²⁴ This was a retrospective study which looked at bacterial meningitis in neonates, children and adults. The total number of children from 0 – 12 years was 41. The most common organism isolated among this age group was *S. pneumoniae*.²⁴ Significantly there was no penicillin resistance among these isolates.²⁴

Developed countries

The most common causative organism of neonatal meningitis in the United States of America, as documented by two studies was group B streptococci.^{9,10} This too was the case in a 10 year retrospective study conducted in the United Kingdom.²⁵

The three studies from the USA, included in this literature review also looked at the impact of preventative strategies, most notably the introduction of the Hib vaccine and the pneumococcal conjugate 7 – serotype vaccine (PCV7). The median age of meningitis was found to have shifted from 15 months to 25 years old after the introduction of the Hib vaccine.⁹ The proportion of cases due to *H. Influenzae* decreased from 58% to 15% after the introduction of the Hib vaccine⁸ *S Pneumoniae* was the predominant organism in infants and young children whereas *N. Meningitidis* was the predominant causative organism in bacterial

meningitis in older children.^{9,10} Antibiotic sensitivity patterns were reported on in one American study.⁹ 9/12 (75%) of *H.influenzae* isolates tested were sensitive to ampicillin. Of the *S. pneumoniae* isolates tested, 54/84 (12 %) were resistant to penicillin.⁹ The rates of bacterial meningitis were found to have decreased sharply among children after the introduction of PCV 7.¹⁰

Three studies from Europe were included in this literature review. One study exclusively dealt with neonates and its findings have already been reported on above.²⁵ A 32 year study conducted in Greece found that *N. Meningitidis* was the most common causative organism among infants and young children (incidence rate = 8,9/ 100 000 children) followed by *S. pneumoniae* (incidence rate 1,3/ 100 000 children).²⁶ The incidence rate of *H. influenzae* declined after the introduction of the Hib vaccine.²⁶ This was in contrast to a study conducted in Lithuania where the most common causative organism was *H. Influenzae*.¹³

The last article looked at from a developed nation was conducted in Korea.²⁷ This 10 year retrospective study concluded that the most common causative organism among neonates was Group B streptococci. The two most common organisms responsible for bacterial meningitis in infants beyond the neonatal period and children were *S. pneumoniae* and *H. influenzae*.²⁷ The rates of *H. influenzae*, however reduced by a third after the introduction of the Hib vaccine.²⁷

Discussion

Acute bacterial meningitis is an important cause of morbidity and mortality among newborns and children.¹ It is thus imperative that one understands the epidemiology of acute bacterial meningitis. It is also important to establish whether certain preventative measures have had an impact on the burden of acute bacterial meningitis.

Causative organisms: Neonates

In the neonatal period the most common causative agents are group B streptococci and the gram negative bacilli. The only African study which deviated from this trend was the study conducted in the Gambia where *S. pneumoniae* was the most common causative organism in neonatal meningitis.²¹ Significantly it seems that group B streptococcal infection is a disease of the developed and developing world. The use of intra partum antibiotics in women in the USA has not reduced the risk of late – onset (older than 7 days) group B streptococcal disease but it has reduced the risk of early onset infection.¹⁰ The South African study reporting on neonatal meningitis stated that 35% of the group B streptococcal infections occurred before 72 hours of age and that it was responsible for 48% of all cases of neonatal meningitis presenting within 7 days of age. It failed to state the percentage of group B streptococci presenting after 7 days of age.¹⁴ One, could, however deduce that the implementation of intra – partum antibiotics in women who screened positive for group B streptococci in South Africa could in the future prevent almost half of the cases of early onset neonatal meningitis. The African studies failed to make a distinction between early and late onset group B streptococcal meningitis.^{18,23}

Causative organisms: older children

Unlike neonatal meningitis, the causative organisms in childhood meningitis varied from region to region. In South Africa four studies reported that *N. meningitidis* was the most common causative organism of childhood meningitis.^{11,12,15,17} One of the Western Cape studies¹¹, however was conducted during a time when Cape Town was experiencing a meningococcal outbreak²⁸. This could explain the preponderance of meningococcal meningitis. None of these four studies were conducted in the era of Hib and PCV7. One author stated that the implementation of the Hib and pneumococcal vaccines would reduce

the incidence of acute bacterial meningitis and that their use be recommended.¹⁵ The most recent study was conducted in the era of the Hib vaccine.¹⁶ The incidence of *H. influenzae* was only 1 %.¹⁶

The other African studies found a different pattern. They found that *S. pneumoniae* and *H. influenzae* were the most common causative organisms in childhood meningitis. The authors of the African articles made a strong case for the implementation of the Hib and pneumococcal conjugate vaccines.¹⁸⁻²³ A substantial amount of meningitis would have been prevented and the burden of disease in already stretched health care services would have been alleviated.^{19,23} Two articles, however, did state that in their studies the *H. influenzae* and *S. pneumoniae* strains were not serotyped and thus it did make it difficult to say whether or not the Hib and pneumococcal conjugate vaccines would have reduced meningitis caused by these two organisms.^{18,20}

In the developed world countries included in this literature review, there was also a difference in the distribution of the causative organisms of childhood meningitis. The USA articles found that *S. pneumonia* and *N. meningitidis* were the most common organisms. These articles, however, only looked at a limited number of causative organisms.⁸⁻¹⁰ Europe only contributed to 3 articles (one of which only reported on neonatal meningitis) in this literature review so it would not be wise to generalise their findings to the whole continent. The Greek study, however, was a large study and it showed trends in bacterial meningitis over 32 years.²⁶ *N. meningitidis* was the most common organism isolated. This study illustrated the impact of the Hib vaccine with a significant reduction of *H. influenzae* meningitis after its introduction.²⁶

The most common causative organism in childhood meningitis in the two Asian articles was *S. pneumoniae*.^{24,27} *H. influenzae* was the second most common organism isolated in the Korean study. This study, did, however, like the Greek study, find that the Hib vaccine

reduced the incidence of *H. influenzae* meningitis.²⁷ This sentiment was re iterated in the USA studies.^{8,9} The only study which was conducted during the era of PCV7 vaccination did find a reduction in the rates of bacterial meningitis in children aged 1 to 23 months old.¹⁰ These findings show the importance of these two vaccines in reducing childhood bacterial meningitis.

Antibiotic susceptibility

As with the differences in distribution of causative organisms throughout the world, there are also differences in antibiotic sensitivity patterns. In South Africa there is a significant *S. pneumoniae* resistance to penicillin in Johannesburg¹⁷, whereas the Cape Town study which reported on *S. pneumoniae* sensitivity found that none of the isolates were resistant to penicillin¹². The Johannesburg study was conducted over two years and looked at bacterial meningitis in patients (from neonates to adults) at 5 hospitals.¹⁷ Seventeen pneumococcal isolates were tested and 8/17(48%) were resistant to penicillin.¹⁷ The Cape Town study was a 3 year hospital based survey and it looked at meningitis only in children up to 13 years old.¹² In this study none of the 28 pneumococci isolated were resistant to penicillin.¹² The Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS –SA) has published surveillance reports in the communicable diseases surveillance bulletin. GERMS –SA has found an increase in pneumococcal resistance to ceftriaxone and penicillin.²⁹ It found that Gauteng had 11% resistance to penicillin, whereas the Western Cape had 8% resistance. GERMS –SA in fact advises that if pneumococcal meningitis is suspected, vancomycin be added.²⁹

In Africa *H. influenzae* has a high resistance against chloramphenicol.^{18,22,23} In fact the Kenyan authors have recommended that children at risk of *H. influenzae* meningitis should be treated with a third generation cephalosporin and not with their first line antibiotics of penicillin and chloramphenicol.¹⁸

Conclusion

This literature review demonstrates that there is a geographical variation in the causative organisms of childhood bacterial meningitis. This too, is true for the patterns of antibiotic sensitivities. It is, thus, important to have a good understanding of the epidemiology of acute bacterial meningitis in one's own region so as to adequately treat this disease. There are credible preventative strategies available, most notably the Hib and pneumococcal vaccines. These should be widely implemented so as to reduce the burden of disease caused by acute bacterial meningitis.

University of Cape Town

References

1. Kim S, Acute Bacterial meningitis in infants and children. *Lancet infect dis* 2010;**10**:32-42
2. Coovadia HM, Wittenberg DF. *Paediatrics and Child Health. A manual for health professionals in developing countries. Fifth Edition.* Cape Town, Oxford University Press 2005
3. Wright P, Approaches to prevent acute bacterial meningitis in developing countries. *Bulletin of the World health organization* 1989; **67**(5): 479 -486
4. Chavez – Bueno S, McCracken G, Bacterial Meningitis in Children. *Pediatr Clin N Am* 2005; **52**: 795 - 810
5. Saez- Llorens X, McCracken G, Bacterial Meningitis in children. *Lancet* 2003; **361**: 2139 - 2148
- 6 Van de Beek D, Brouwer MC , Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. *Lancet* 2012; **380**:1703 - 11
- 7 Standard treatment guidelines and essential drug list for South Africa Hospital level Paediatrics. Pretoria 2006
8. Neuman HB, Wald ER, Bacterial Meningitis in Childhood at the Children’s Hospital of Pittsburgh: 1988 – 1998. *Clinical Pediatrics* 2001; **40**: 595 -600
9. Schuchat A, Robinson K, Wenger J et al, Bacterial Meningitis in the United States in 1995. *The New England Journal of medicine* 1997; **337**(14): 970 -976
10. Thigpen MC, Whitney CG, Messonnier NE, et al, Bacterial Meningitis in the United States, 1998 – 2007. *The New England Journal of Medicine* 2011; **364**(21): 2016 - 2025
11. Potter PC, Donald PR, Moodie J, Slater C, Kibel MA. Meningitis in Cape Town children. *SAMJ* 1984; **66**:759 -762
12. Donald PR, Burger PJ, Becker WB, Paediatric meningitis in the Western Cape. A 3 – year hospital – based prospective survey. *SAMJ* 1986 ;**70**: 391- 395
13. Narkeviciute I, Bernatoniene J, Mikeliuonyte A et al , Aetiological diagnostics of acute bacterial meningitis in children. *Scandinavian Journal of Infectious Diseases*, 2006; **38**: 782 -787
- 14 .Nel E. Neonatal Meningitis: Mortality, Cerebrospinal Fluid, and Microbiological Findings. *Journal of Tropical Pediatrics* 2000; **46**: 237 - 238
15. Hussey G, Schaaf H, Hanslo D et al, Epidemiology of post – neonatal bacterial meningitis in Cape Town children. *SAMJ* 1997; **87**(1): 51 - 56
- 16 Wolzak NK, Cooke ML, Orth H, van Toorn R. The changing profile of Paediatric meningitis at a referral centre in Cape Town, South Africa. *Journal of Tropical Pediatrics* 2012 **58** (**6**): 491 - 495
17. Liebowitz LD, Koornhof HJ, Barrett M, Bacterial Meningitis in Johannesburg – 1980 – 1982. *SAMJ* 1984; **66**:677- 679
18. Mwangi IM, Berkley J, Lowe B, et al. Acute bacterial meningitis in children admitted to a rural Kenyan hospital: increasing antibiotic resistance outcome. *The Pediatric Infectious Disease Journal* 2002; **21**(11): 1042 - 1048
19. Roca A, Bassat Q, Morais L et al. Surveillance of Acute Bacterial Meningitis among Children admitted to a District Hospital in Rural Mozambique. *Clinical Infectious Diseases* 2009; **48**: S172 - 180
20. Siguaque B, Roca A, Sanz S, et al. Acute bacterial meningitis among children , in Manhica, a rural area in Southern Mozambique. *Acta Tropica* 2008; **105**: 21 -27

-
21. Palmer A, Weber M, Bojang K, McKay T, Adgebola R. Acute Bacterial Meningitis in The Gambia: A Four – year Review of Paediatric Hospital Admissions. *Journal of Tropical Pediatrics* 1999; **45**: 51 -53
 22. Bercion R, Bobossi- Serengbe G, Gody JC et al, Acute Bacterial Meningitis at the ‘ Complex Pediatrique’ of Bangui, Central African Republic. *Journal of Tropical Pediatrics* 2007;**54**(2): 125-128
 23. Molyneux E, Walsh A, Phiri A, Molyneux M. Acute bacterial meningitis in children admitted to the Queen Elizabeth Central Hospital, Blantyre, Malawi in 1996 – 97. *Tropical Medicine and International Health* 1998; **3**(8): 610 -618
 24. Mani R, Pradhan S, Nagarathna S, Wasiulla R, Chandramuki A. Bacteriological profile of community acquired acute bacterial meningitis: A ten – year retrospective study in a tertiary neurocare centre in South India. *Indian Journal of Medical Microbiology*, 2007: **25**(2): 108 - 114
 25. Holt DE, Halket S, de Louvois J, Harvey D, Neonatal Meningitis in England and Wales: 10 years on. *Arch Dis Child Fetal Neonatal Ed* 2001; **84**: F85- F89
 26. Theodoridou MN, Vasilopoulou VA, Atsali EE et al, Meningitis registry of hospitalized cases in children: epidemiological patterns of acute bacterial meningitis throughout a 32- year period. *BMC Infectious Diseases* 2007; **7**:101
 27. Cho HK, Lee H, Kang JH, Kim KN, et al, The Causative organisms of Bacterial Meningitis in Korean Children in 1996 – 2005. *J Korean Med Sci* 2010; **25**: 895 – 899
 28. Ryder CS, Beatty DW, Heese HD. Group B meningococcal infection during an epidemic in Cape Town , South Africa. *Ann Trop Paediatr* 1987;**7**: 47-53
 29. Respiratory & Meningeal Pathogens Reference Unit, National institute for Communicable diseases. *Communicable Diseases Surveillance Bulletin*. May 2010: 34 – 43

Non- Tuberculosis culture confirmed bacterial meningitis in South African neonates, infants and children 2005 – 2010.

Dr KM Thomas: Paediatric registrar, School of child and adolescent health, University of Cape Town

Prof M Levin: Head of Allergy Services; Red Cross Children's War Memorial Hospital, Cape Town

Mr H Carrara: Biostatistician; University of Cape Town

University of Cape Town

Abstract:**Background:**

Acute bacterial meningitis is an important cause of morbidity and mortality in new-borns and children. Knowing the epidemiological pattern of acute bacterial meningitis in a specific area will help health professionals to initiate the best empiric antibiotic therapy.

Methods:

This was a retrospective descriptive and analytical cohort study. The subjects of this study were patients in the paediatric population from 0 to 12 years who had positive cerebrospinal fluid (CSF) cultures due to bacteria from 2005 – 2010. All provinces, whose data was captured on the Corporate Data Warehouse (CDW) during this time, were included. (The CDW is a public laboratory system in South Africa recording all culture results.)

Results:

The sample size was 6030.

In neonates the most common causative organisms were Gram negative bacilli : 32.1%; 95% CI: 29.4% - 34.8% (n/N = 378/1178) and Group B Streptococcus : 30.5%; 95% CI: 27.9% – 33.1% (n/N= 359/1178) . Listeria monocytogenes contributed 0.2%. (n/N= 2/1178)

S. pneumoniae was the most common causative organism in children > 3 months.

The prevalence of S. pneumoniae prior to the conjugate pneumococcal vaccine was 40.3% while after the introduction the prevalence was 21%. (p – Value < 0.001)

Conclusion:

The most common causative organisms in the neonatal period were gram negative bacilli and group B streptococci. S. pneumoniae was the most common causative organism of bacterial meningitis among South African children > 3 months. The advent of the conjugate pneumococcal vaccine has seen a decrease in the prevalence of S. pneumoniae.

Keywords: bacterial meningitis, children, neonates, new – borns, South Africa

Introduction

Bacterial meningitis is an important cause of morbidity and mortality in new-borns and children.¹

In South Africa the fatality rate among infants and children due to meningitis is between 3 and 7%.² Developing countries have a higher mortality as well as different epidemiological patterns compared to developed countries.³ Knowing the most common causes of bacterial meningitis in various age groups helps health professionals to initiate the best empiric antibiotic therapy.^{1,4,5} Previous studies conducted in South Africa looked at subjects from only one province (either the Western Cape or Gauteng).^{6,7,8,9,10,11} The most common cause of childhood bacterial meningitis reported by four of the studies was Neisseria meningitidis^{6,7,9,10} while the organisms most commonly responsible for neonatal meningitis were Gram negative bacilli and group B streptococci.^{7,8,10} These studies also demonstrated a higher prevalence of Penicillin resistant Streptococcal pneumoniae isolates in Johannesburg compared to the Western Cape.^{7,10} The most recent South African study found that the commonest non mycobacterium cause of bacterial meningitis was S. pneumoniae.¹¹ This study also found that antibiotic pre – treatment may have resulted in an underestimation of CSF culture – positive meningococcal cases.¹¹

The Haemophilus B (Hib) vaccine was introduced in South Africa in 1999 while the pneumococcal conjugate vaccine was included in the South African vaccine schedule on 1 April 2009. Children born after 15 February 2009 were eligible for the conjugate

pneumococcal vaccine.¹² The role out of the pneumococcal vaccine was, however unequal in each province.

The aim of this study was to investigate the aetiology of non - Tuberculosis bacterial meningitis in South African new-borns and children from 2005 – 2010 and to assess the change in prevalence of organisms prior to and after the introduction of the conjugate pneumococcal vaccine.

Methods:

This was a retrospective descriptive and analytical cohort study.

Subjects

The subjects of this study were patients in the paediatric population (0 – 12 years of age) who had positive cerebrospinal fluid (CSF) culture results from 2005 – 2010. All provinces, whose data was captured on the Corporate Data Warehouse (CDW) during this time, were included. (The CDW is a public laboratory system in South Africa recording all culture results.)

This sample represented the paediatric population who made use of government hospital in South Africa.

Data

Data was obtained from the CDW. All provinces except for Kwazulu Natal were included. (Kwazulu Natal's data was not captured on the CDW for the time period of this study). The following data was requested: all positive non Tuberculosis bacterial CSF culture results (from age 0 – 12) from 1 January 2005 to 31 December 2010, the date of birth, the date when the CSF specimen was taken, the name of the hospital and ward from where the CSF sample was sent and details of all antibiotic susceptibility testing. The data obtained stated sensitivity

or resistance to a particular antibiotic and the method of ascertaining susceptibility was not stated. Even though only date of birth was requested the CDW did give the age of each patient. The CDW defined age in days, months and years.

This study did not include positive blood cultures or subjects with probable meningitis but not proven on CSF culture.

Inclusion criteria:

- All positive non Tuberculosis bacterial CSF culture results (from age 0 – 12) from 1 January 2005 to 31 December 2010

Exclusion criteria:

- Positive CSF cultures due to Mycobacterium tuberculosis and fungi were.
- Patients who had no age documented.
- Patients older than 12 years.

Measurement

A database was created in Microsoft excel onto which variables of interest were entered: patient number, age of patient when sample taken, date when sample taken, organism grown, antibiotic name, susceptibility, province of origin, hospital name, ward from which specimen taken.

Analyses

Descriptive analyses were done in Excel. Statistical analyses were performed using StataIC version 11. The proportion of causative organisms per age group was calculated for the overall sample. The proportion of causative organisms was then calculated for each calendar year. Early neonatal period was defined as age 0 – 7 days old whereas the late neonatal period was defined as > 7 days old. The proportions of group B streptococcus in the early vs late neonatal period were calculated. The relative proportions of causative organisms prior to and after the introduction of the conjugate pneumococcal vaccine were calculated. Years

2005 – 2008 were defined as ‘pre vaccine’ and years 2009 – 2010 were defined as ‘post vaccine’. The chi-squared test was used to assess difference in prevalence and proportions before and after the introduction of the conjugate pneumococcal vaccine. Antibiotic resistance and susceptibility patterns were described. The level of significance for all analyses was $p \leq 0.05$.

Results:

Sample

Seven thousand eight hundred and eighteen samples were obtained from the CDW.

Unfortunately 1504 had no date of births and were defined as 0 days, 0 months and 0 years, 57 were over 12 years of age, 11 were due to *Candida*, 5 were due to *Cryptococcus* and 211 were due to *M. tuberculosis*. These were excluded and this left a total sample size of 6030.

(Figure 1) The distribution among the years was as follows: 2005:411; 2006:1186;

2007:1140; 2008: 1135; 2009:1090; 2010: 1068.

The break down per age group was:

1. 0 – 28 days: 1178
2. 1 – 3 months: 711
3. > 3 months to 5 years: 3166
4. > 5 years – 12 years:975

Organisms by age group from 2005 - 2010

Neonatal period (0 – 28 days)

In the neonatal group the most common causative organisms were Gram negative bacilli: 32.1%; 95% CI: 29.4% - 34.8% (n/N= 378/1178) and group B streptococcus 30.5%; 95% CI: 27.9% – 33.1% (n/N= 359/1178). The majority (73.5%) of group B streptococcus occurred after 7 days whereas 26.5% occurred in the early neonatal period. Coagulase negative staphylococci (CONS) was the third most common causative organism contributing 12.6%;

95% CI: 10.7% - 14.5% (n/N= 148/1178). Listeria monocytogenes only contributed 0.2% (n/N=2/1178). (See figure 2)

1-3 months:

The 1 – 3 month group had a different distribution of organisms with Gram negative bacilli contributing 31.1%; 95% CI: 27.7% - 34.5% (n/N= 221/711) and S.pneumoniae 23.4%; 95%: CI 20.2% - 26.5%(n/N= 166/711). (See figure 3)

>3 months – 5 years:

S. pneumoniae: 44.6%; 95% CI: 42.9% – 46.4%(n/N= 1413/3166) was the most common organism in the 3 month – 5 year age group. Gram negative bacilli accounted for 17.6 %; 95% CI: 16.3% - 18.9% (n/N= 557/3166) while CONS comprised 10.9% ; 95% CI: 9.8% - 12% (n/N = 344/3166). Neisseria meningitidis and Haemophilus influenzae contributed 8.1% ; 95% CI: 7.1% – 9% (n/N= 255/3166) and 4.5% ;95% CI: 3.7% -5.2% (n/N= 141/3166) respectively. (See figure 4)

> 5 years – 12 years:

S. pneumoniae :55.5%; 95% CI: 52.4% – 58.6% (n/N= 541/975) emerged as the most common organism in the >5 – 12 year age group. Gram negative bacilli contributed 10.1%; 95% CI: 8.2% - 11.9% (n/N= 98/975) while N. meningitidis and H.influenzae accounted for 7.90% ;95% CI 6.2% – 9.6% (n/N = 77/975) and 2.7% ;95% CI: 1.7% – 3.7% (n/N= 26/975) respectively. Coagulase negative staphylococci also featured with a prevalence of 10.9% ; 95% CI: 9.8% - 12%(n/N= 106/975). (See figure 5).

A chi square test showed that the difference in distribution of organisms per age group and per year was statistically significant (p –value < 0.001).

The following graphs show the change of prevalence of each organism per year and per age group. (Figures 6 – 18).

Proportion of causative organisms pre- and post the conjugate pneumococcal vaccine:

Of the 6030 samples, 1102 were eligible for the vaccine. Table 1 depicts the prevalence of causative organism pre – and post the conjugate vaccine era, as percentages of total cases of meningitis. (See Table 1).

Table 2 depicts the difference between the absolute yearly number of organisms from 2006 – 2008 compared to 2009 – 2010 (the vaccine era). The year 2005 was excluded due to the limited amount of CSF samples from that year. (See Table 2).

Antibiotic susceptibilities:

Table 3 shows the antibiotic susceptibilities of the important causative organisms. (See Table 3)

Discussion

Causative organisms

There is a difference in distribution of common causative organisms according to age.

Neonates (0 – 28 days)

The chief causes of acute bacterial meningitis in this age group were gram negative bacilli and group B streptococci. This is in keeping with international^{4, 5} and national literature.⁸ The prevalence of the gram negative bacilli decreased in 2009 and 2010 whereas the prevalence of group B streptococci remained steady over the 5 years. The significant contribution of the group B streptococci raises the possibility that the implementation of intrapartum antibiotic therapy in women who are positive for group B streptococci might have decreased the prevalence of neonatal meningitis. In the United States of America (USA) the use of intrapartum antibiotics reduced the risk of early but not late onset infection.^{13, 5} Unfortunately the bulk of group B streptococcal meningitis occurred in the late neonatal period and thus the use of intrapartum antibiotics might not have had a marked effect. Other preventative measures such as the immunisation of mothers with group B streptococcal conjugate vaccine

is a strategy that is being considered in other settings.⁵ L. monocytogenes is a very rare cause of meningitis in our setting, accounting for 0.17%. This is in keeping with a previous South African study on neonatal meningitis which found only one L. monocytogenes isolate.⁸ The third most common causative organism in this age group is the coagulase negative staphylococci (CONS). Although CONS are usually regarded as contaminants, in sick neonates they should be considered as pathogens.¹⁴ One can only assume that the neonates included in this study were ill enough to warrant a lumbar puncture and that the CONS isolated were in fact, significant.

1 – 3 months:

This age group represents an interim period between the neonatal period and early childhood. The most common causative organisms were the gram negative bacilli and S. pneumoniae. International guidelines state that empiric antibiotic therapy in this age group should include ampicillin to cover for L. monocytogenes.¹ Interestingly, of the six L. monocytogenes isolated, none of them were cultured in this age group.

>3 months – 5 years:

The most common causative organism in this age group was S. pneumoniae. This is in keeping with studies conducted in the USA as well as a recent South African study^{11,13,15} This is, however, in contrast to older South African studies which revealed that N. meningitidis was the most common causative organism among children.^{6,7,9,10} Antibiotic pre-treatment may have resulted in an underestimation of CSF culture – positive meningococcal cases. This was seen in a recent South African study.¹¹

The prevalence of S. pneumoniae remained above 40% from 2005 to 2009 with a reduction to 34.62% in 2010. ($p = <0.001$) This could be explained by the introduction of the conjugate pneumococcal vaccine in 2009 as well as the effect of anti-retroviral therapy. An antiretroviral program was initiated in South Africa in 2004.¹⁶ A recent study showed that

the antiretroviral program was associated with a significant decline in the burden of invasive pneumococcal disease among children infect with Human Immune Deficiency virus (HIV)¹⁶. H. influenzae B (Hib) only accounted for 4.45%. This is most likely due to the immunization of infants with the Hib vaccine which was implemented in 1998. Surveillance for invasive Hib disease in South Africa has shown a significant decrease since the introduction of the Hib vaccine.¹² Coagulase negative staphylococci accounted for 10.87%. Unfortunately, the technique and circumstances in which the CSF samples were collected was not documented in this study. The presence of coagulase negative staphylococci could indicate poor sterile technique, specimen collection to culture delay, errors with laboratory sequencing or a nosocomial infection. There was insufficient data to exclude nosocomial meningitis. The prevalence of HIV in South Africa among children aged 2 – 14 in 2008 was 2.5%¹⁷ This could account for the marked presence of the gram negative bacilli and coagulase negative staphylococci in this age group.

>5 years to 12 years:

S. pneumoniae is the commonest organism isolated. This is again, in contrast to previous South African studies which found that N. meningitidis was the commonest cause of acute bacterial meningitis among children.^{6,7,9,10} The prevalence of this organism remained steady at >50% over the five years. Patients in this age group were not eligible for the conjugate pneumococcal vaccine and thus its impact was not seen in this age group. N. meningitidis was the fourth most common causative organism after S. pneumoniae, coagulase negative staphylococci and the gram negative bacilli. H. influenzae was not very prevalent in this group. Its prevalence was half than its presence in the 3 month to 5 year age group. An unexpected finding is the significant presence of gram negative bacilli and coagulase negative staphylococci, which again, raises concern about the sterility of lumbar punctures and

laboratory practices. The underlying health of the patients was also not known. It would be interesting to see what the immune status of these patients was and if these two organism groups occurred mainly in immunosuppressed individuals.

Antibiotic susceptibility:

It must be emphasized that not all isolates were tested for antibiotic susceptibility. Each specific isolate per organism group was also not necessarily tested for susceptibility against the same antibiotics. The data obtained stated sensitivity or resistance to a particular antibiotic and the method of ascertaining susceptibility was not stated. Unfortunately the CDW does not reflect centralised testing but rather testing as done by all the regional national health laboratory services (NHLS) laboratories .

The following empiric treatment regimes for bacterial meningitis are recommended: < 1 month: ampicillin plus either gentamicin or cefotaxime; 1 – 3 months: ampicillin plus either cefotaxime or ceftriaxone (add vancomycin if pneumococcal meningitis is suspected) ; 3months – 21 years: Either cefotaxime or ceftriaxone plus either vancomycin or rifampicin (in areas with a high incidence of resistant S. pneumoniae)¹

The most common causative organisms in the neonatal age group were gram negative bacilli and group B streptococci. Of the group B streptococci that were tested, 98.88% were susceptible to penicillin/amoxicillin/ampicillin. The gram negative bacilli had only 56.4% susceptibility against gentamicin. This group had higher susceptibility (> 80%) against amikacin and meropenem. A proportion of isolates may not be covered with first line antibiotics. It may be prudent when dealing with gram negative bacilli to consider changing antibiotics. The gram negative bacilli had a high resistance against third generation cephalosporins. This may indicate nosocomial gram negative infection.

Current recommendations are for Ampicillin to be added in meningitis treatment regimens to cover for L. monocytogenes. All 6 isolates were susceptible to penicillin/ampicillin/

amoxicillin. This rare cause of meningitis in South Africa will therefore be covered by current antibiotic regimes.

Numerous S. pneumoniae isolates (1104) were tested for susceptibility against the third generation cephalosporins with a 98.46% sensitivity and 1789 isolates were tested for susceptibility against Penicillin/Ampicillin/Amoxicillin with a 70.88% susceptibility. This data therefore supports the use of empiric third generation cephalosporin for treatment of childhood meningitis. The Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS – SA), however still recommends that Vancomycin be added if pneumococcal meningitis is suspected.¹⁸ Apart from outliers in 2005 N. meningitidis and H. influenzae both had high rates of susceptibility to third generation cephalosporins.

The impact of the conjugate pneumococcal vaccine:

The 7 – valent conjugate pneumococcal vaccine was introduced into the South African vaccination schedule in 2009.¹² Children born after 15 February 2009 were eligible for the vaccine and no catch up immunisation was planned.¹² Unfortunately this study looked at data from 2005 – 2010 and thus there were fewer samples collected in the post vaccine era. Nonetheless, the data revealed that there was a statistically significant reduction in the prevalence of S. pneumoniae meningitis from 40.29% in the pre vaccine era to 20.96% in the post vaccine era (p – value < 0.001). A similar finding was reported by GERMS – SA which found that there was a decrease in invasive pneumococcal disease in infants less than 1 year in 2009.¹⁸ This was attributed to the introduction of the conjugate pneumococcal vaccine that same year.¹⁸ It would be interesting to look at more extensive data dating from the point of the conjugate vaccine introduction to present day. One would hope that the early trend of declining S. pneumoniae prevalence would continue. It is however, prudent to remember that

the 7 – valent vaccine may lead to a shift in prevalent pneumococcal serotypes and this may be a threat to vaccine success. With this in mind the 13 – valent conjugate pneumococcal vaccine was introduced into the South African vaccination schedule in 2012. Further research may reveal whether this vaccine will have additional impact.

With the decline in S. pneumoniae meningitis there was an increase in some of the other organisms. Those that significantly increased were: coagulase negative staphylococci, enterococci, Methicillin resistant S. aureus, group B streptococcus and the gram negative bacilli. This however, may be an artefact due to the declining number of S. pneumoniae isolates causing a lower denominator.

Limitations:

This data was obtained from a data warehouse. There is no information on how the specimens were collected. Not all organisms isolated were tested for antibiotic sensitivities. The data obtained stated sensitivity or resistance to a particular antibiotic and the method of ascertaining sensitivity was not stated. Although the number of specimens collected were fairly similar from 2006 – 2010, there were far fewer samples collected in 2005, when the progress was just beginning. There was insufficient data to determine the prevalence of nosocomial infections and the amount of positive CSF cultures from neurosurgical wards. There was no data on the HIV status of the subjects. All gram negative organisms were grouped together.

Conclusion:

The most common causative organisms in the neonatal period are gram negative bacilli and group B streptococci. L. monocytogenes is a rare cause of acute bacterial meningitis among South African newborns and children. S. pneumoniae is the most common causative organism of bacterial meningitis among South African children > 3months. The conjugate pneumococcal vaccine has significantly decreased the absolute prevalence and the relative proportion of S. pneumoniae meningitis.

Funding: No funding was required.

Conflict of interest: None declared

University of Cape Town

Figure 1: Logarithm of CSF disposition

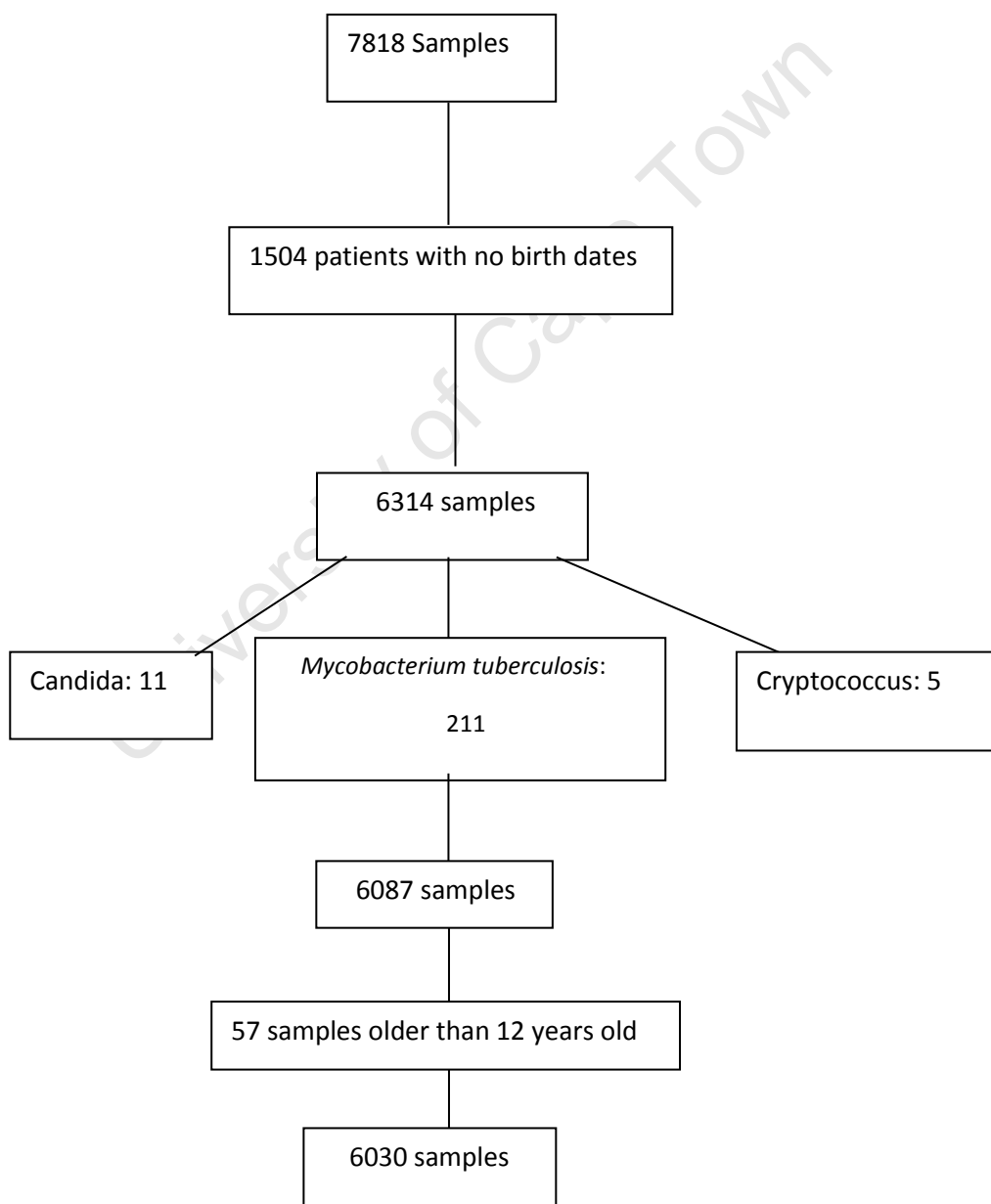


Figure 2:

Prevalence of causative organisms in the neonatal period from 2005 to 2010 (error bars depict the 95% confidence interval)

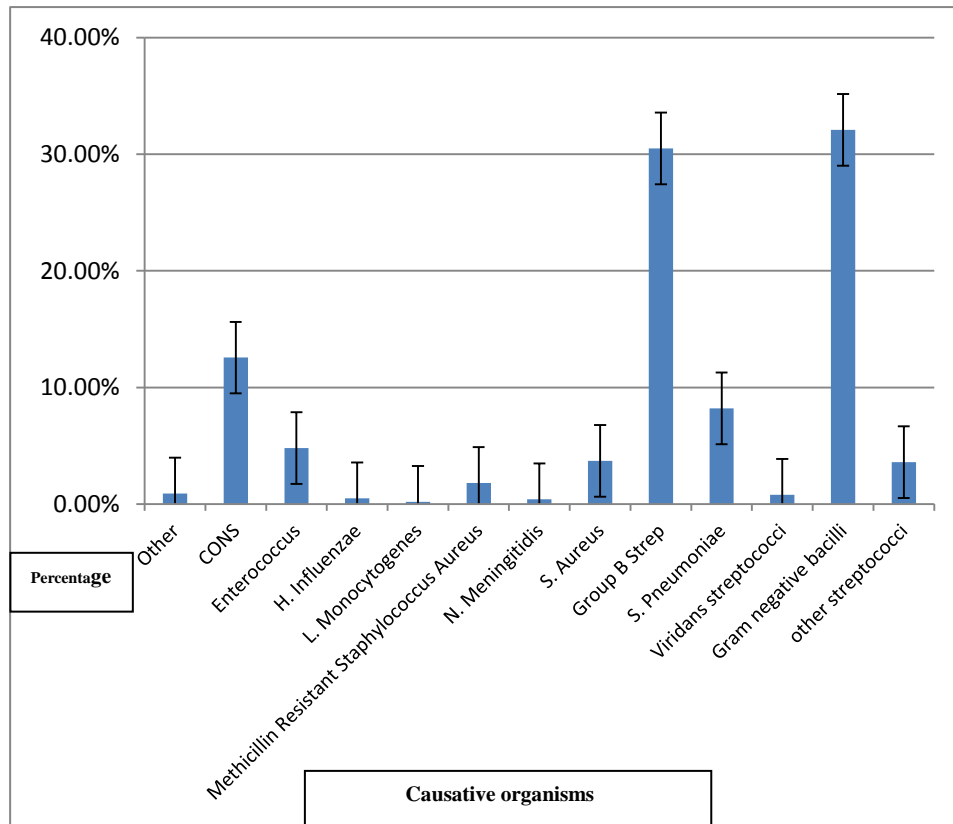


Figure 3: Prevalence of causative organisms among infants aged 1 – 3 months from 2005 to 2010

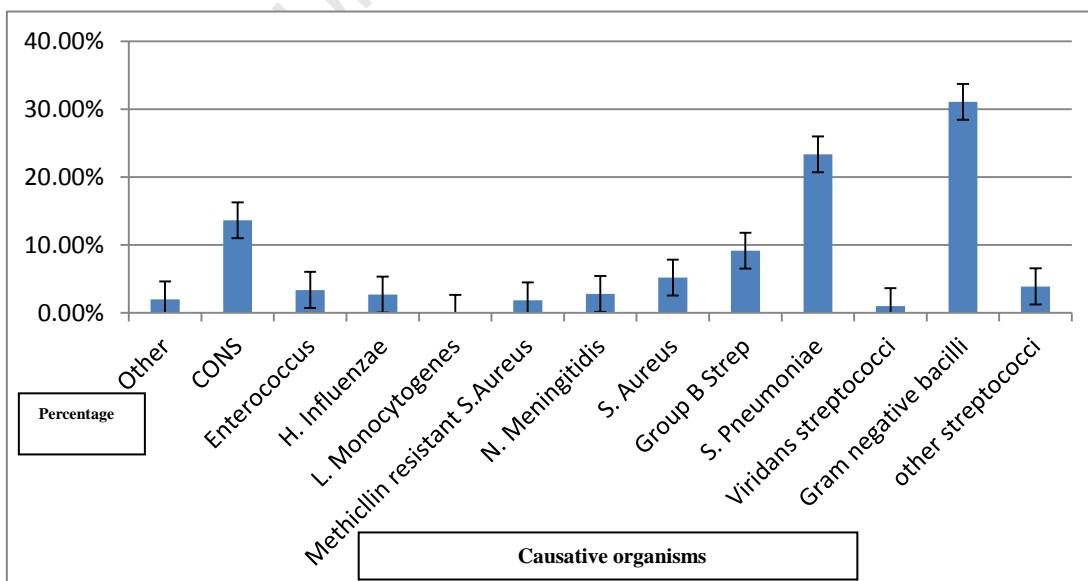


Figure 4: Prevalence of causative organisms among infants and children aged >3 months to five years from 2005 to 2010

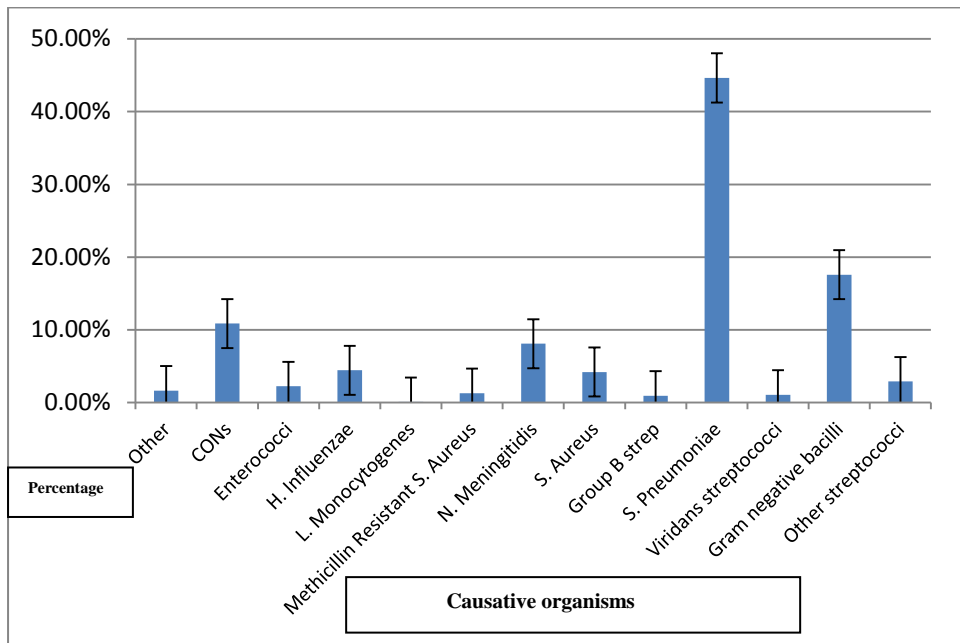


Figure 5: Prevalence of causative organisms among children aged >5 to 12 years from 2005 to 2010

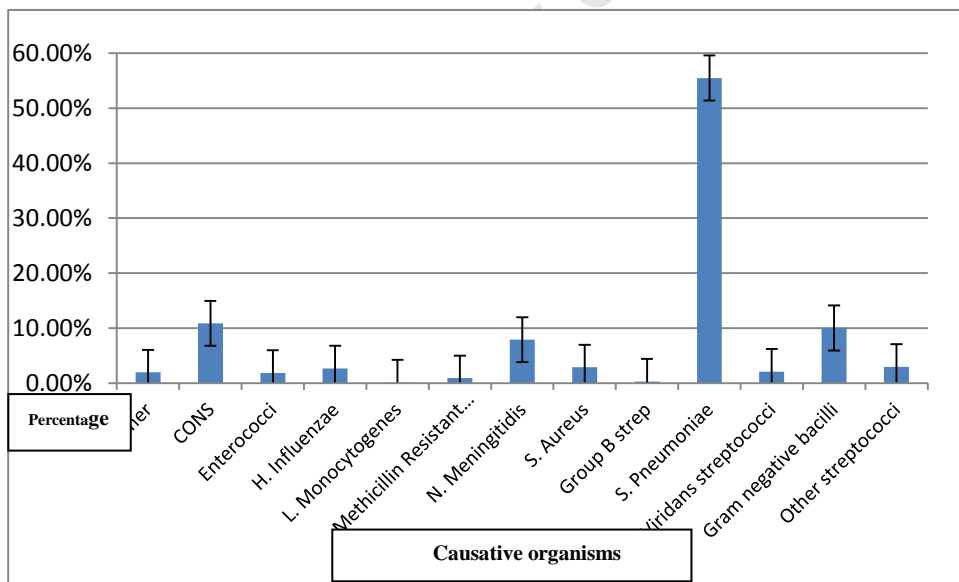


Figure 6: Distribution of the coagulase negative Staphylococci per age group and per year

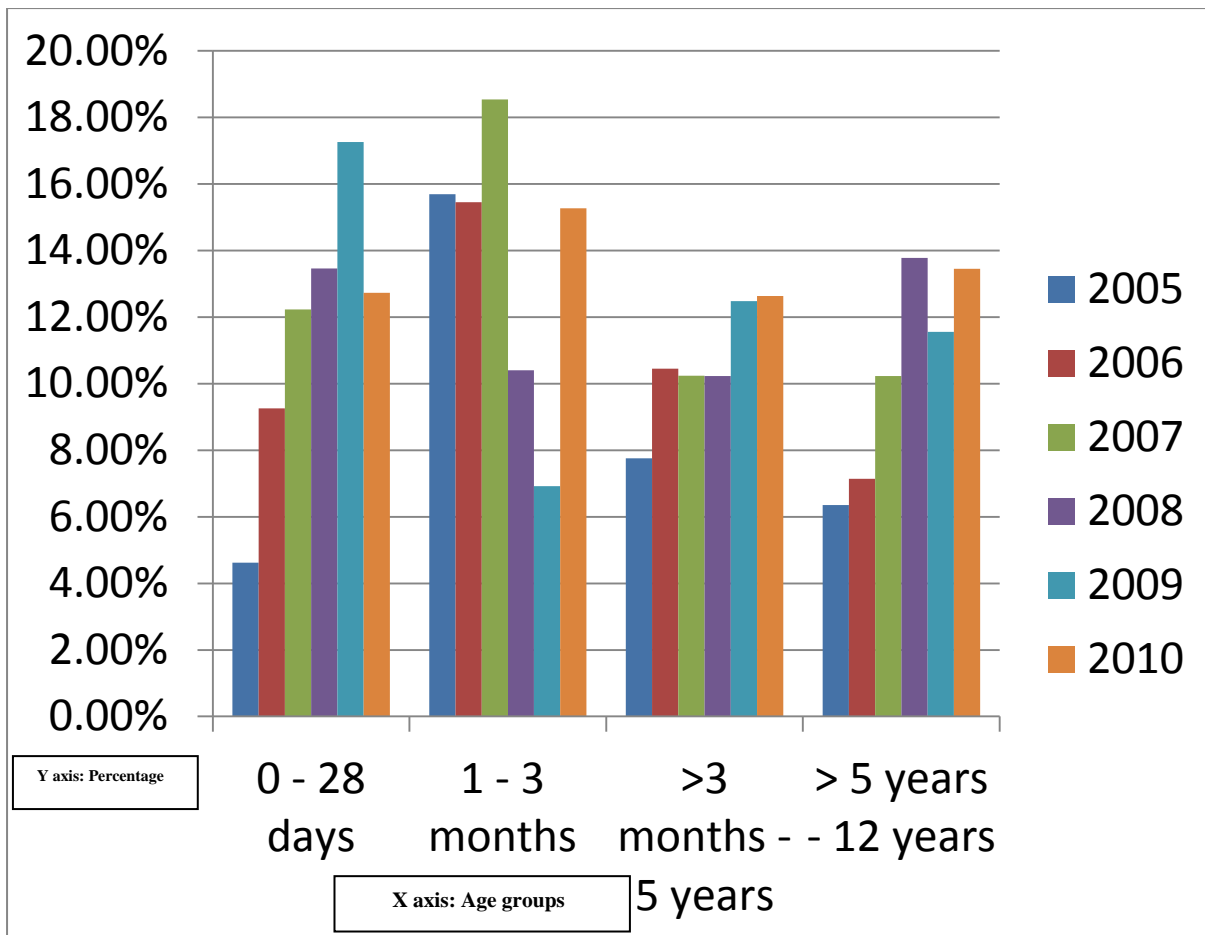


Figure 7: Distribution of Enterococci per age group and per year

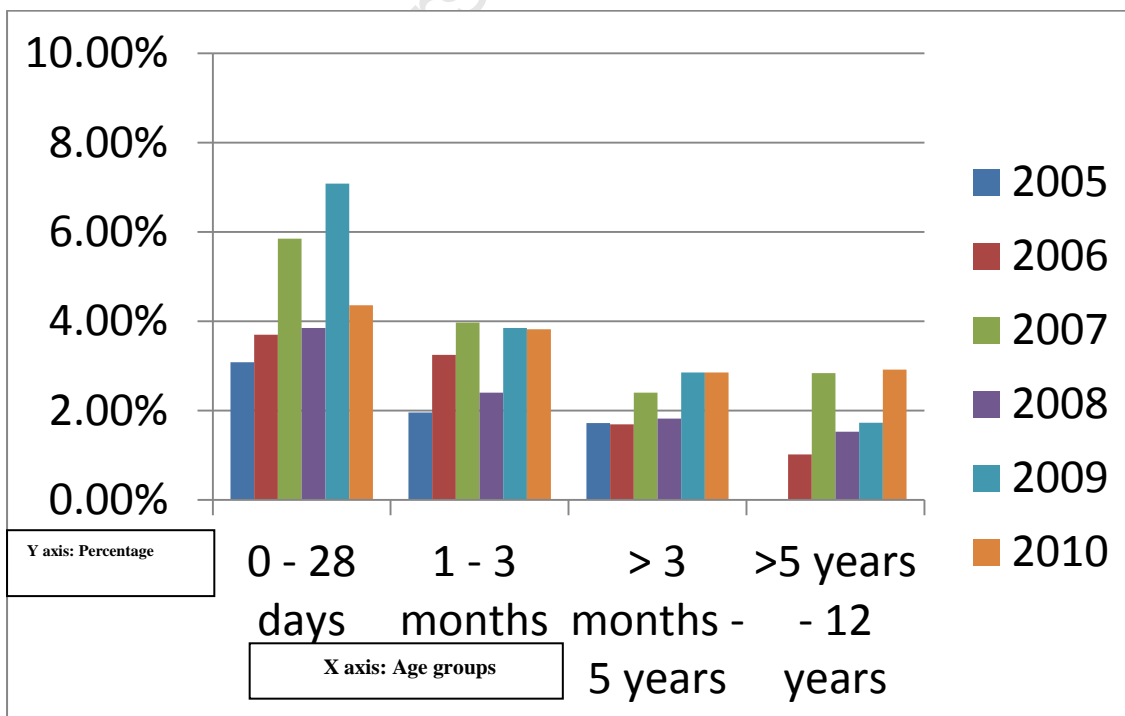


Figure 8: The distribution of the Gram negative bacilli per age group and per year

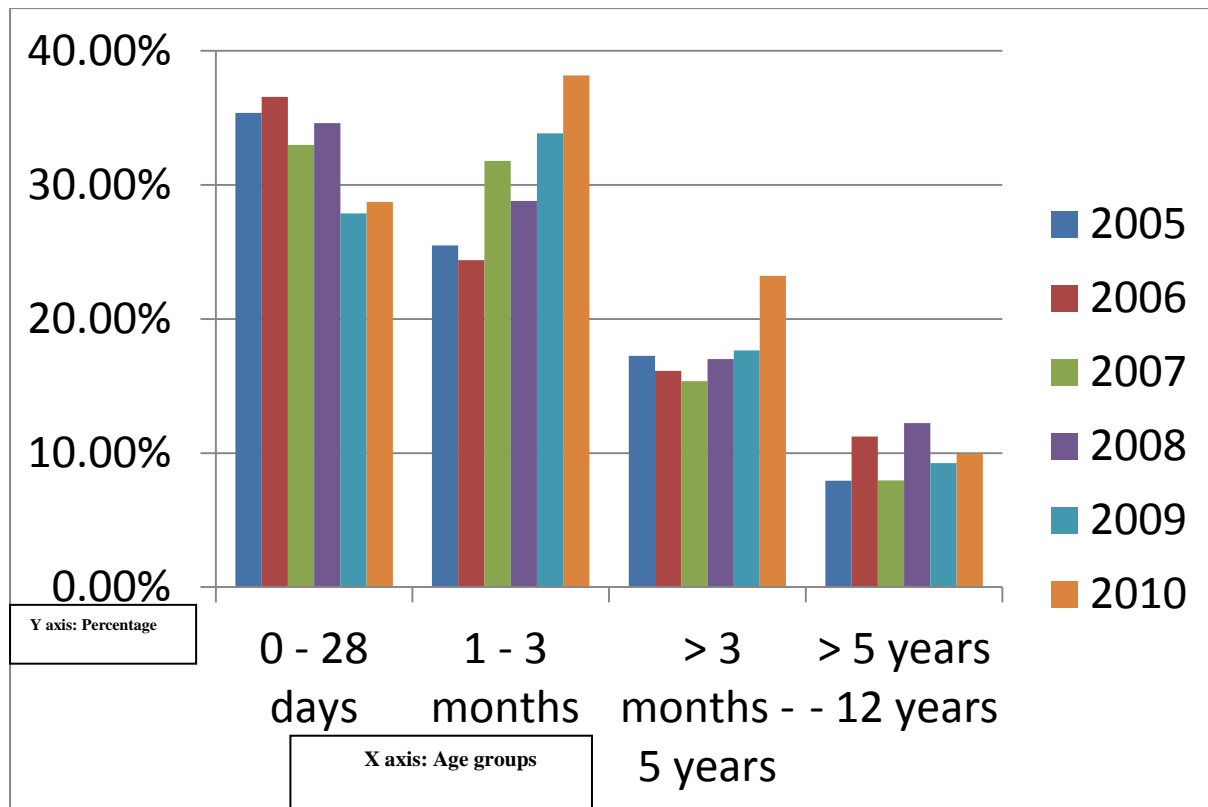


Figure 9: The distribution of group B streptococcus per age group and per year

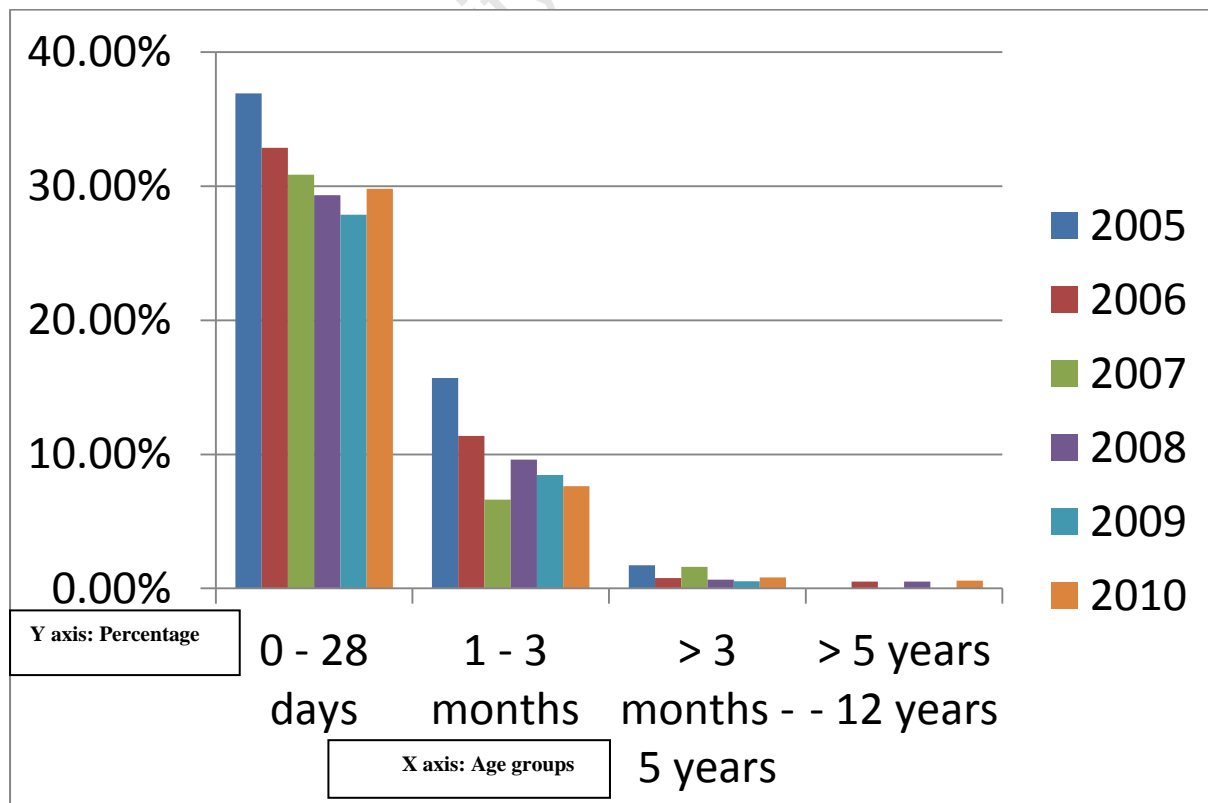


Figure 10: The distribution of *H. influenzae* per age group and per year:

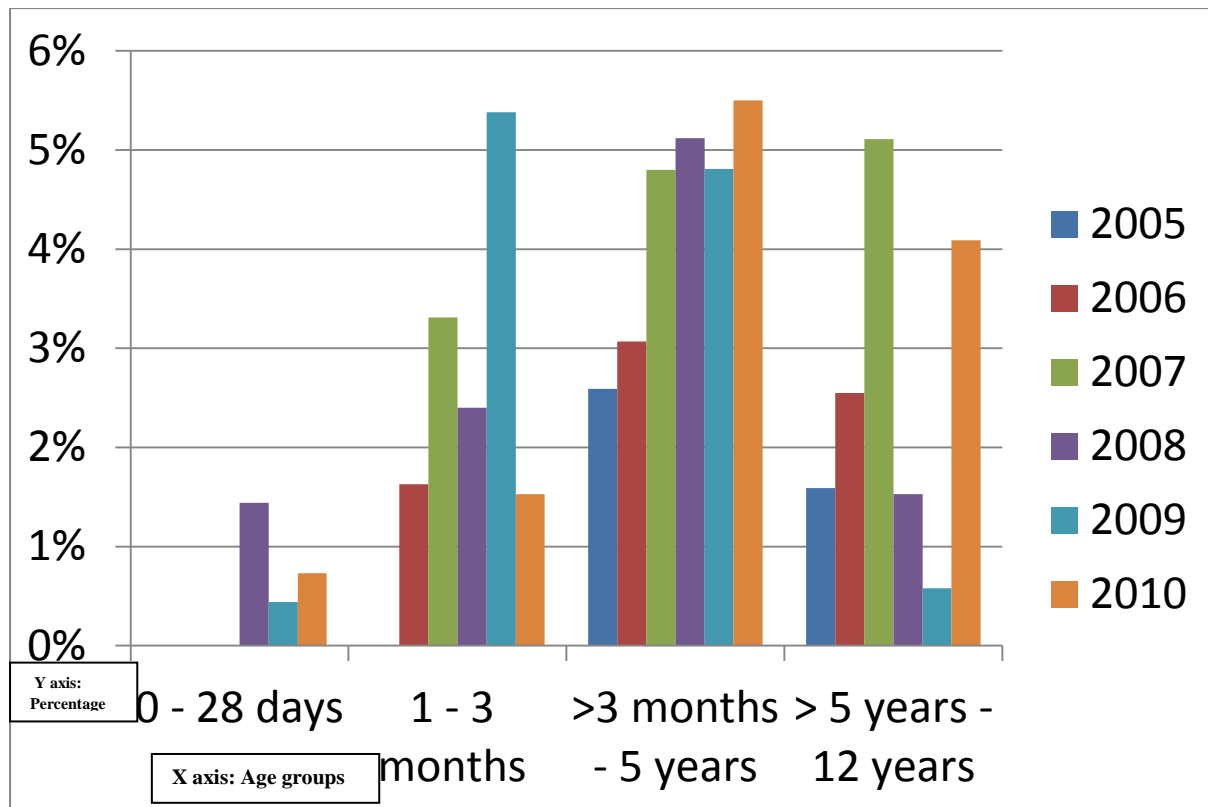


Figure 11: The distribution of *L. monocytogenes* per age group and per year:

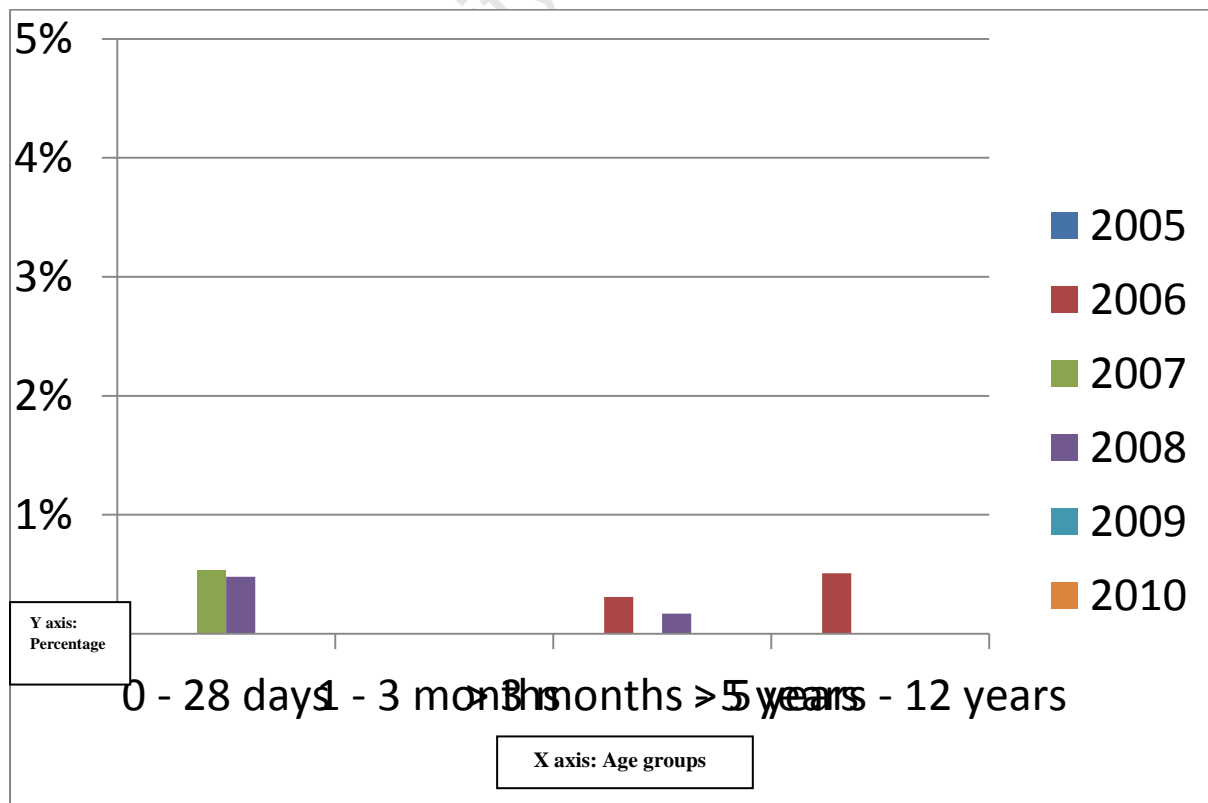


Figure 12: The distribution of Methicillin resistant *S. aureus* (MRSA) per year and per age group

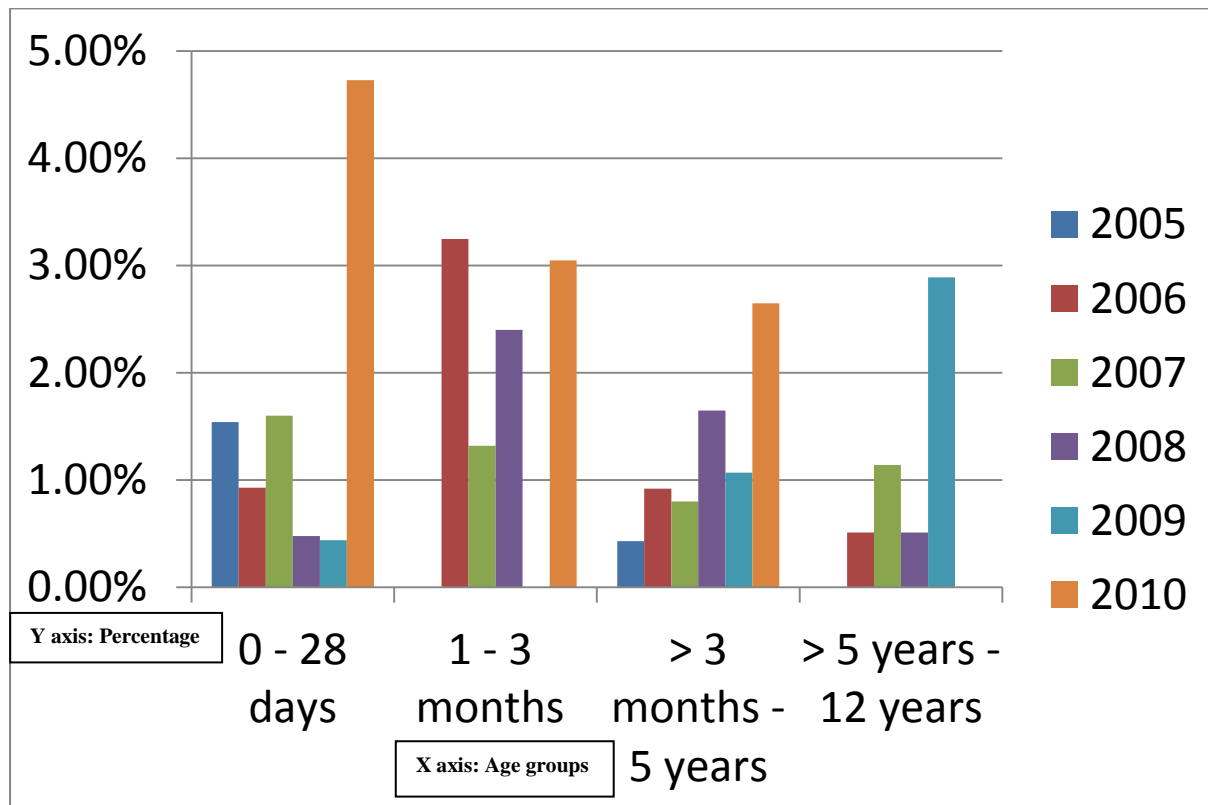


Figure 13: The Distribution of *N. meningitidis* per age group and per year

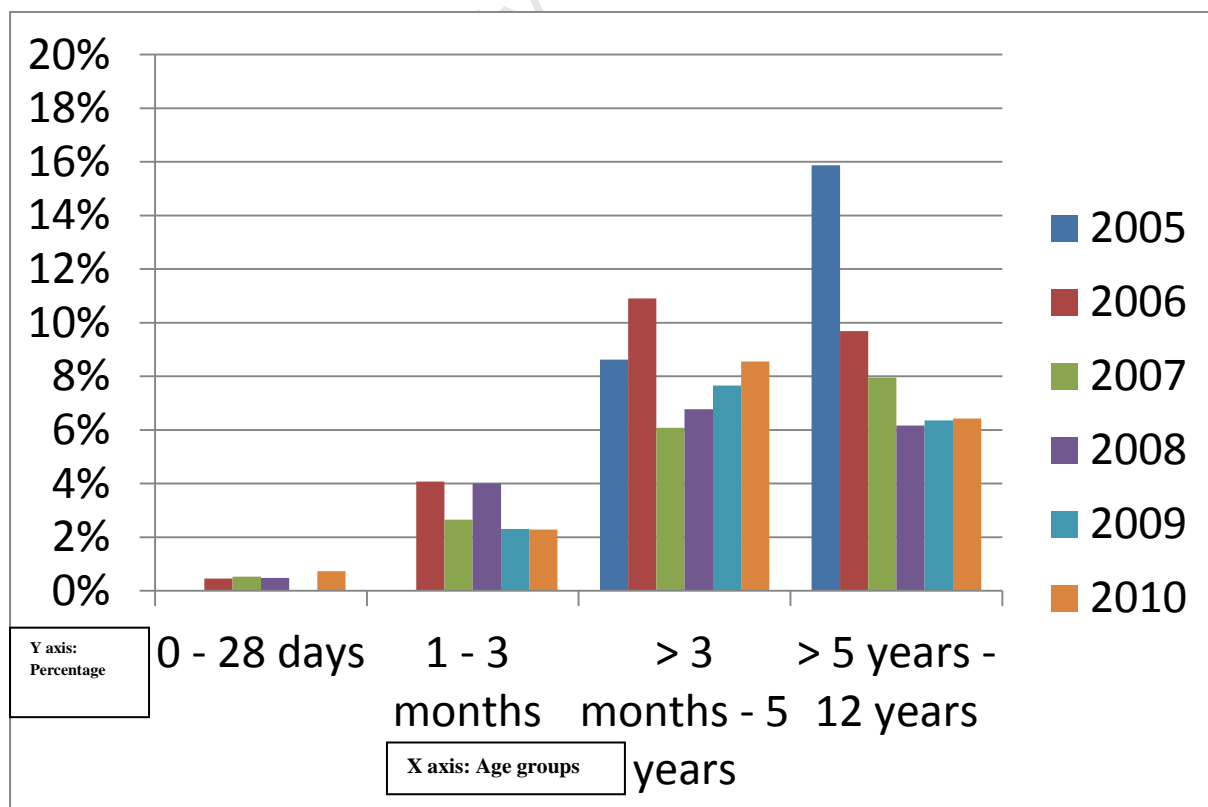


Figure 14: The distribution of *Staphylococcus aureus* per age group and per year

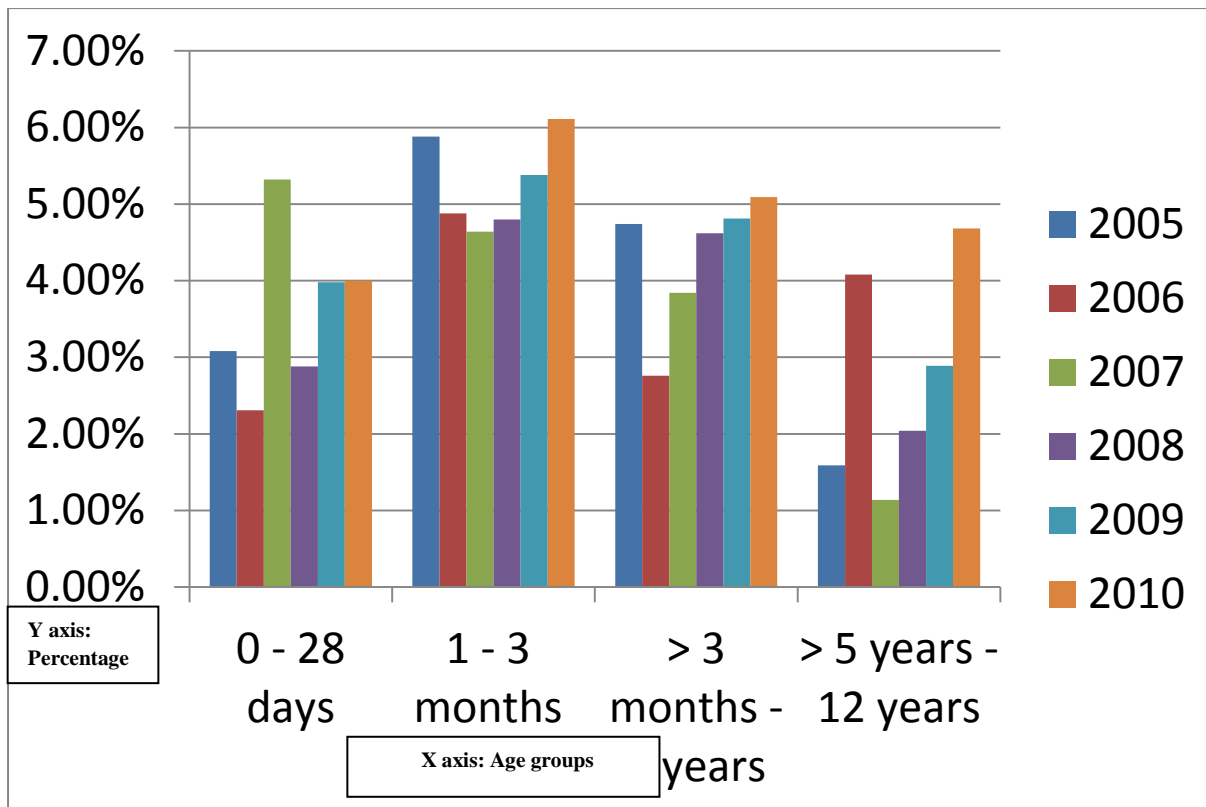


Figure 15: The distribution of *S. pneumoniae* per age group and per year

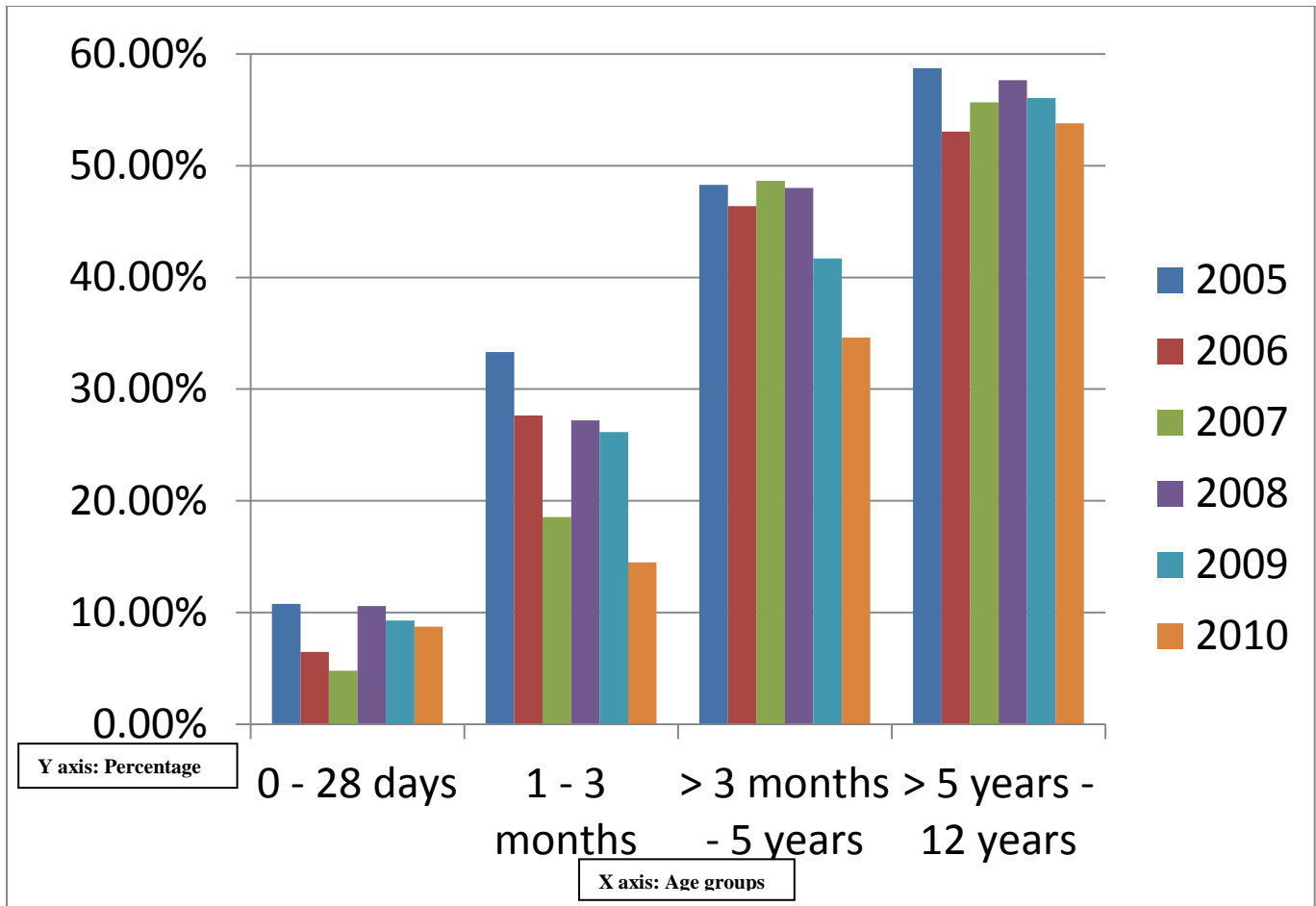


Figure 16: The distribution of Viridans streptococci per age group and per year

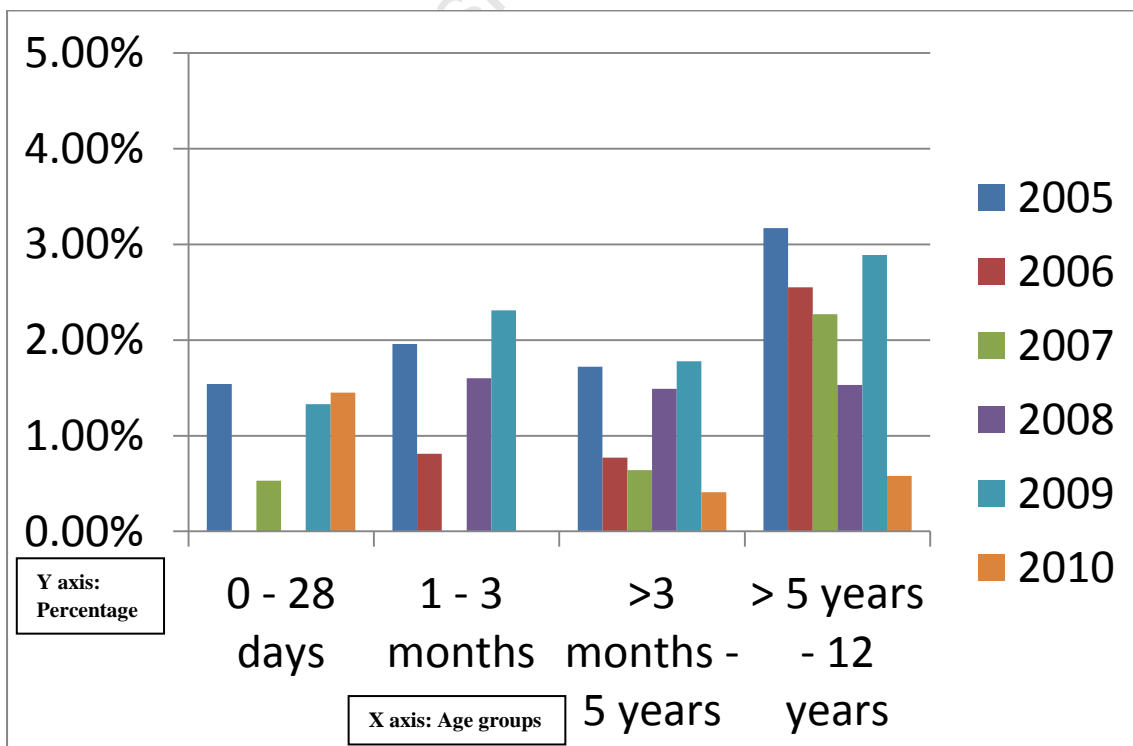


Figure 17: The distribution of other streptococci per age group and per year

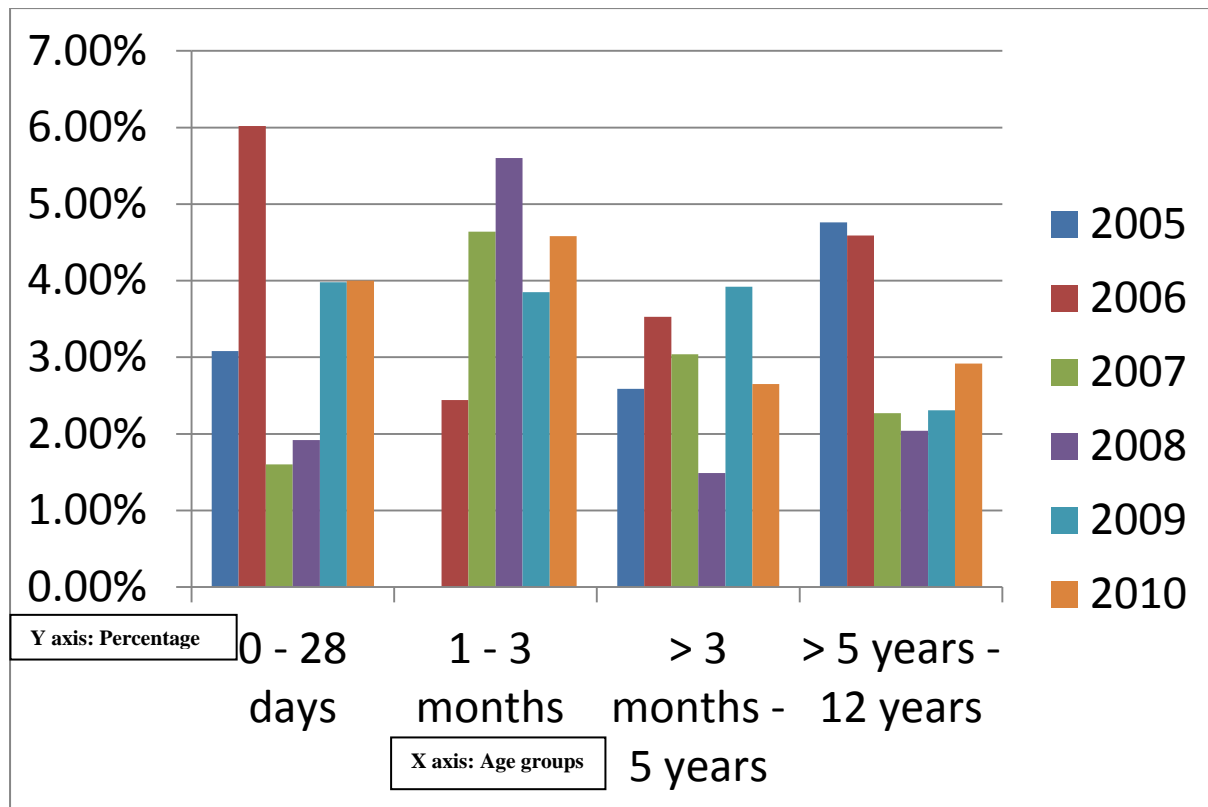


Figure 18: The distribution of other organisms per age group and per year

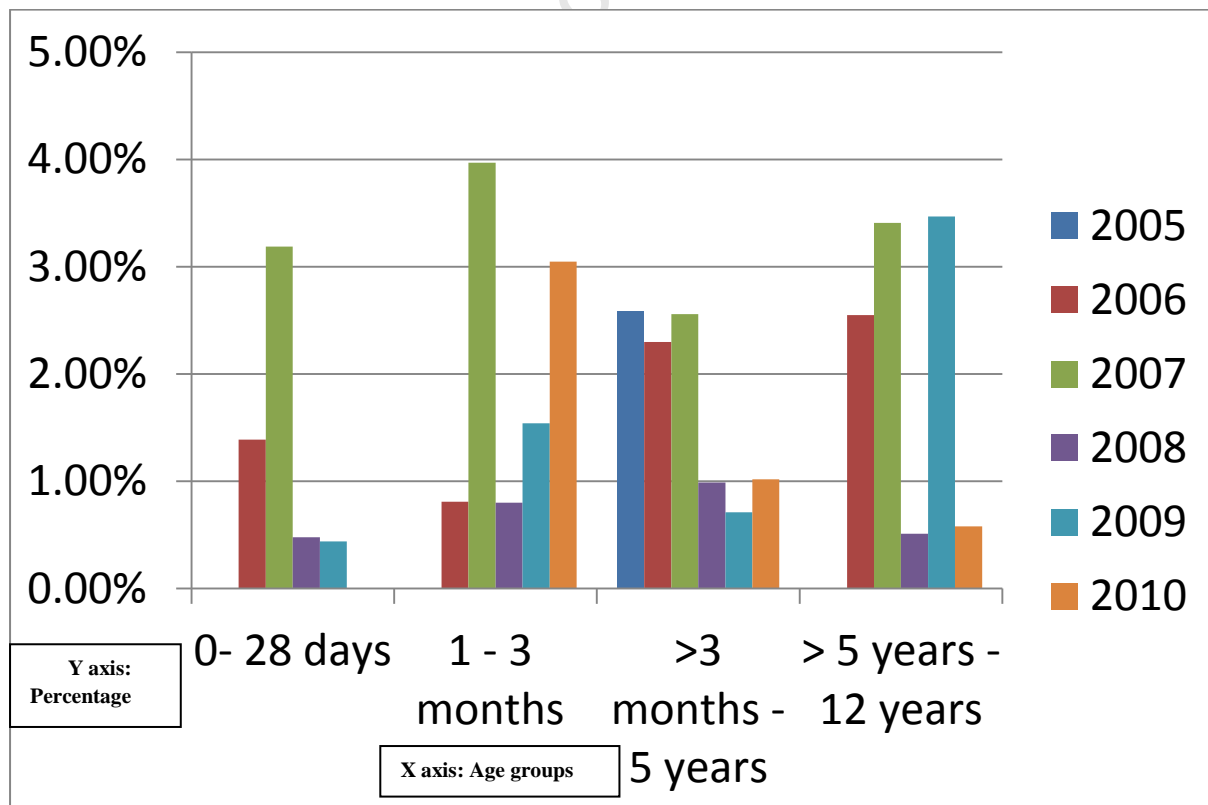


Table 1: The effect of the conjugate pneumococcal vaccine:

Organism	Pre vaccine % (n/N)	95% CI	Post vaccine% (n/N)	95% CI	P – value
Coagulase Negative Staphylococcus (CONS)	11.1% (548/4929)	10.2% - 12%	13.3% (147/1102)	11.3 % - 15.4%	0.037
Enterococci	2.5% (124/4929)	2.1% - 3%	4.2% (46/1102)	3% - 5.3%	0.003
Gram negative bacilli	19.3% (951/4929)	18.2% - 20.4%	27.6% (304/1102)	24.9% - 30.2%	<0.001
Group B streptococcus	5.9% (291/4929)	5.3% - 6.6%	15.1% (166/1102)	13%-17.2%	<0.001
<u>H. influenzae</u>	3.2% (159/4929)	2.7%- 3.7%	3% (33/1102)	2% - 4%	0.693
<u>L. monocytogenes</u>	0.12% (6/4929)	0.02% - 0.2%	0%		0.247
Methicillin Resistant <u>S. aureus</u> (MRSA)	1.1% (54/4929)	0.8% - 1.4%	2.7% (30/1102)	1.8% - 3.7%	<0.001
<u>N. meningitidis</u>	6.6% (321/4929)	5.8% - 7.2%	3.3% (36/1102)	2.2% - 4.3%	<0.001
<u>S. aureus</u>	3.9% (193/4929)	3.4% - 4.5%	4.4% (48/1102)	3.2% - 5.6%	0.5
<u>S. pneumoniae</u>	40.3% (1986/4929)	38.9%- 41.7%	21% (231/1102)	18.6% - 23.4%	<0.001
Streptococcus viridans	1.2% (60/4929)	0.9% - 1.5%	0.9% (10/1102)	0.4% - 1.5%	0.385
Other streptococci	3% (150/4929)	2.6% - 3.5%	3.7% (41/1102)	2.6% - 4.8%	0.246
Other	1.7% (86/4929)	1.4%- 2.1%	0.9%(10/1102)	0.4%-1.5%	0.045

Table 2: The effect of the conjugate pneumococcal vaccine from years 2006 - 2010

Organism	Pre vaccine	Average no per year (2006 – 2008)	95% CI	Post vaccine	Average no per year (2009 – 2010)	95% CI	P-value
Coagulase negative staphylococci (CONS)	11.4%	128	10.5% - 12.3%	13.3%	139	11.3% - 15.4%	0.073
Enterococci	2.5%	29	2.1% - 3.1%	4.2%	38	3% - 5.4%	0.005
Gram negative bacilli	19.3%	230.7	18.1% - 20.4%	27.6%	241	25% - 30.2%	<0.001
Group B streptococcus	5.6%	82.3	5% - 6.3%	15.1%	87	13% - 17.2%	<0.001
<u>H. influenzae</u>	3.4%	37	2.8% - 3.9%	3%	37	2% - 4%	<0.001
<u>L. monocytogenes</u>	0.1	2	0.03% - 0.2%	0%	0	N/A	0.226
MRSA	1.2%	13.3	0.8% - 1.5%	2.7%	21	1.8% - 3.7%	<0.001
<u>N. meningitidis</u>	6.4%	70.7	5.7% - 7.2%	3.3%	57.5	2.2% - 4.3%	<0.001
<u>S. aureus</u>	3.9%	41.3	3.3% - 4.5%	4.4%	50	3.2% - 5.6%	0.484
<u>S. pneumoniae</u>	40.1%	451	38.7% - 41.6%	21%	345.5	18.6% - 23.4%	<0.001
Streptococci viridans	1.2%	10.4	0.8% - 1.5%	0.9%	5	0.4% - 1.5%	0.488
Other streptococci	3.1%	35	2.6% - 3.6%	3.7%	37.5	2.6% - 4.8%	0.276
Other	1.8%	22.3	1.4% - 2.2%	0.9%	11.5	0.4% - 1.5%	0.073

Table 3: Antibiotic susceptibilities:

Organism	Antibiotic	Total number tested	Sensitivity 2005	Sensitivity 2006	Sensitivity 2007	Sensitivity 2008	Sensitivity 2009	Sensitivity 2010	Total Sensitivity
Gram negative bacilli	Amikacin	679	87.1%	83.8%	76.3%	85.6%	84.1%	85.8%	83.5%
	Gentamicin	883	64.5%	58.6%	54.7%	56.7%	53.6%	54.1%	56.4%
	Meropenem	604	92.9%	93.8%	82.4%	84.1%	88.4%	88.5%	87.9%
	Third generation cephalosporins	1067	68.1%	62.9%	65.2%	57.5%	53.4%	56.1%	59.8%
Group B Streptococci	Penicillin/ Amoxicillin/ Ampicillin	447	100%	95.5%	100%	98.7%	100%	100%	98.9%
<u>H.influenzae</u>	Third generation cephalosporins	149	60%	90.9%	100%	96.8%	100%	96.6%	96%
<u>L. monocytogenes</u>	Penicillin/ Amoxicillin/ Ampicillin	6	No organisms	100%	100%	100%	No organisms	No organisms	100%
<u>N.meningitidis</u>	Third generation cephalosporins	264	95.7%	100%	100%	100%	100%	100%	99.6%
	Penicillin/ Amoxicillin/ Ampicillin	328	96.6%	97.8%	98.2%	98%	90.2%	100%	97%
<u>S.pneumoniae</u>	Penicillin / Amoxicillin/ Ampicillin	1789	76.3%	72.7%	66.3%	72.7%	71.2%	67.6%	70.9%
	Third generation cephalosporins	1104	97%	98.1%	98.3%	97%	99.5%	99.3%	98.5%

References:

1. Kim S. Acute Bacterial meningitis in infants and children. *Lancet Infect dis* 2010;**10**:32-42
2. Coovadia HM, Wittenberg DF. Paediatrics and Child Health. A manual for health professionals in the developing world. Fifth Edition. Cape Town Oxford university Press 2003
3. Wright PF. Approaches to prevent acute bacterial meningitis in developing countries. *Bulletin of the World Health Organization* 1989; **67** (5): 479 - 486
4. Chavez – Beuno S, McCracken G. Bacterial Meningitis in Children. *Pediatr Clin N Am* 2005; **52**: 795 - 810
5. Saez – Llorens X, McCracken G. Bacterial Meningitis in children. *Lancet* 2003; **361**: 2139 -2148
6. Potter PC, Donald PR, Moodie J, Slater C, Kibel MA. Meningitis in Cape Town Children. *SAMJ* 1984; **66**:759 - 762
7. Donald PR, Burger PJ, Baecker WB. Paediatric meningitis in the Western Cape. A 3 - year – hospital - based prospective survey. *SAMJ* 1986; **70**: 391 - 395
8. Nel E. Neonatal Meningitis: Mortality, Cerebrospinal Fluid, and Microbiological Findings. *Journal of Tropical Pediatrics* 2000; **46**: 237 -238
9. Hussey G, Schaaf H, Hanslo D et al. Epidemiology of post neonatal bacterial meningitis in Cape Town children. *SAMJ* 1997; **87**(1):51 - 56
10. Liebowitz LD, Koornhof HJ, Barret M. Bacterial Meningitis in Johannesburg – 1980 – 1982. *SAMJ* 1984; **66**:677- 679
11. Wolzak K, Cooke ML, Orth H, van Toorn R. The Changing Profile of Pediatric Meningitis at a Referral Centre in Cape Town, South Africa. *Journal of Tropical Pediatrics* 2012; **58**(6):491-495
12. Vonn Gottberg A. Bacterial Meningitis in the era of pediatric vaccination against the encapsulated pathogens. *CME* 2010; **28** (6): 252 - 259
13. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial Meningitis in the United States, 1998 – 2007. *The New England Journal of Medicine* 2011; **364** (21) : 2016 - 2025
14. Kloos WE, Bannerman TL. Update on Clinical Significance of Coagulase – Negative Staphylococci. *Clinical Microbiology Reviews* 1994; **7** (1): 117 - 140
15. Schuchat A, Robinson K, Wenger J et al. Bacterial Meningitis in the United States in 1995. *The New England Journal of Medicine* 1997; **337** (14) : 970 – 976
16. Nunes Mc, von Gottberg A, de Gouveia L, Cohen C, Moore DP, Klugman KP, Madhi SA. The impact of antiretroviral treatment on the burden of invasive pneumococcal disease in South African children: a time series analysis. *AIDS* 2011; **25**: 453 - 462
17. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Pillay, van Wyk V, Mbelle N, Van Zyl J, Parker W, Zungu NP, Pezi S & the SABSSM III Implementation Team; South African national HIV prevalence, incidence, behaviour and communication survey 2008: A turning tide among teenagers? Cape Town HSRC Press, 2009
- 18 Respiratory & Meningeal Pathogens Reference Unit, National institute for Communicable diseases. *Communicable Diseases Surveillance Bulletin*. May 2010: 34 - 43



Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: nosi.tsama@uct.ac.za

8 March 2011

HREC REF: 121/2011

Dr K Thomas
Paediatrics
Red Cross Hospital

Dear Dr Thomas

PROJECT TITLE: BACTERIAL MENINGITIS IN NEONATES AND CHILDREN IN SOUTH AFRICA.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above mentioned study.

Approval is granted for one year until 15 March 2012.

Please submit an annual progress report if the study continues beyond the approval period. Alternatively, please submit a brief summary of your findings, so that we can close our records.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

Ntsama

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

FHS017: Annual progress and study closure report

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

1. Protocol information

Date	27/2/2012	
HREC REF Number	121/2011	
Protocol number (if applicable) & Protocol title	Bacterial Meningitis in neonates and children in South Africa	
Principal Investigator	Karla Thomas	
Department / Office Internal Mail Address	Department of paediatrics; karlamthomas@yahoo.com	
1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. Protocol status (tick ✓)

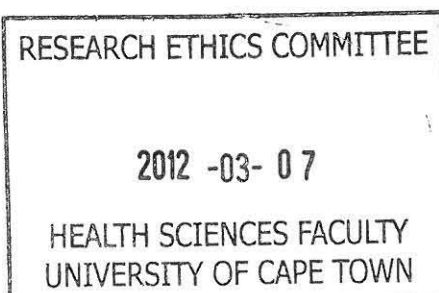
<input type="checkbox"/>	Research-related activities are ongoing
<input checked="" type="checkbox"/>	Data collection is complete, data analysis only
<input type="checkbox"/>	All research-related activities are complete (i.e. final report)

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	6031	
Total number of records or specimens collected, reviewed or stored since last progress	/	
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

Signature of PI	Signature removed	Date	27/2/2012
Signature of Supervisor (if PI is a student)	Signature removed	Date	1/3/12





HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual or final approval, including any documentation described above.			
<input checked="" type="checkbox"/> Approved	Annual progress report		
OR <input type="checkbox"/> Approved	Study closure report		
<input type="checkbox"/> Not approved	See attached comments		
Expiry date	15 MARCH 2013		
Signature Chairperson of the HREC	Signature removed	Date	7.3.12.

pp

RESEARCH ETHICS COMMITTEE
 2012 -03- 07
 HEALTH SCIENCES FACULTY
 UNIVERSITY OF CAPE TOWN

To: Alex Jennings,

Re: Permission to obtain data from the CDW

I am a paediatric registrar at UCT and would like to request data from the CDW from the year 2005 - 2010. I would like to use this data for a MMed study.

I will not require the names of the patients and thus the data will be anonymous. I would, ideally, like to look at data from all provinces whose data is captured on the CDW.

The intent is to examine bacterial meningitis with the following objectives in mind:

- To determine the prevalence (and 95 % confidence interval) of causative organisms of acute bacterial meningitis among culture positive cerebral spinal fluid (CSF) in four paediatric periods namely: 1. The neonatal period (day 0 – 28 days of life); 2. 1 – 3 months; 3. 3 months to 5 years) and 4. Children older than 5 years of age up till 12 years. If, for, example we find that *Listeria* is a relatively rare cause of neonatal meningitis, there is no intent to make any recommendations to change current antibiotic regimes.
- To compare the prevalence of the causative organisms among culture positive CSF and the 95% confidence interval between the various age groups.
- To determine the relative proportions of pneumococcal meningitis prior to and after the introduction of the conjugate pneumococcal vaccine.
- To determine anti biotic resistance and sensitivity patterns among the organisms causing bacterial meningitis in neonates and children.

The data which will be needed:

1. Positive CSF culture results of all children (in the provinces whose data is captured on the CDW) from birth to 12 years for the year 2005- 2010. It would be advantageous if one could look at data from the whole of South Africa, but it is understandable if this is logistically not possible. (If this is the case, then I would just like to look at the data from the Western Cape)
2. Date of birth of each patient
3. The name of the organism grown
4. Date of positive CSF culture
5. Date when CSF specimen was taken
6. The name of hospital (this won't be published but the level of the hospital: ie: district, regional or tertiary might be used)
7. The ward from which the sample was taken
8. Details of all antibiotic sensitivity testing(resistance and sensitivities)

Thank you for your time and attention,

Karla Thomas

karlamthomas@yahoo.com

0832458308

CORPORATE DATA WAREHOUSE DATA REQUEST FORM

Use this form to request new or modified data extracts from the Corporate Data Warehouse

HELPDESK USE ONLY	WORK ORDER NO.	
--------------------------	-----------------------	--

To have this request processed, please log a service request to Helpdesk via email or fax, together with a completed form (email: helpdesk1@nhls.ac.za, FAX: (011)386-6308)

Each application will be approved or rejected subject to the ability to extract this data and the availability of the data, and subject to the intended usage of the requested data.

APPLICANT'S DETAILS

Applicant name	Dr KARLA THOMAS	Tel No	(083)2458308	Email	karlamthomas@yahoo.com
Supervisor name	Dr J A Simpson	Tel No	()	Email	john.simpson@nhls.ac.za
Laboratory/Department (Internal)	NHLS, Greenpoint				
Organisation (external)	National Dept of Health /University of Cape Town				

CONDITIONS

- Data/Information is not to be used in contravention of Sections 14, 15, 16 and 17 of the National Health Act 61 of 2004 and the Promotions of Access to information Act 2 of 2000.
- The Applicant acknowledges that this application is governed by the Data Use Agreement made between the relevant Provincial Department of Health and the NHLS.
- The applicant undertakes to ensure that the data supplied to it by the NHLS is used ethically and solely for the purposes for which was provided as detailed in the application, and further acknowledges that it shall remain liable for any breaches of this clause by the end user.
- If the purpose for the data requested in this application is research, the institute's ethics approval shall be attached to the application form.
- The applicant shall be entitled to include any data and /or information generated in terms of this application, in publications and other presentations only with prior approval by the NHLS.
- The applicant shall give due credit, including affiliation, of the participation of the NHLS in any such publications or presentations.
- The applicant and authorizing authority will be directly liable for any breach of contract.

ACCEPTANCE

*This must be completed for TB, ARV & Cervical screening data programmes

By signing this document we accept the conditions stated on page 1

Applicant	Dr JA Simpson	Signature		Date	/ /20
Supervisor	Dr JA Simpson	Signature		Date	/ /20
APPROVAL BY BUSINESS					
Business Manager	Mr Lunga Makamba	Signature		Date	/ /20
*Programme head	N/A	Signature		Date	/ /20

**CORPORATE DATA WAREHOUSE
DATA REQUEST FORM**

ADDITIONAL INFORMATION		
Region (for data extract e.g Province or Lab prefix)	Western Cape, Eastern Cape, Free state, Guateng, Mpumulanga, Northern Cape, Limpopo, North West Province	
Data range of extract	2005 -2010	
Fields required e.g patient name, DOB, etc.	All positive CSF culture results from ages 0 - 12 years, DOB , hospital and ward where specimen taken, The level of the hospital (ie, district, regional, tertiary), date csf taken, name of organism grown, details of all antibiotic sensitivity testing(resistance and sensitivities)	
FIELD OF DATA		
<input type="checkbox"/> Haematology	<input type="checkbox"/> Anatomical Pathology	<input type="checkbox"/> Virology
<input type="checkbox"/> Chemical Pathology	<input type="checkbox"/> Cytology	<input checked="" type="checkbox"/> Microbiology
<input type="checkbox"/> Other (provide details):		
DESCRIPTION OF REQUIRED DATA		
I would like all positive CSF culture results from children aged 0 - 12 years, the name of the organism grown, the date which the specimen was taken, dob of each patient, the name of hospital (this won't be published), the name of the ward where the specimen was taken, , details of all antibiotic sensitivity testing(resistance and sensitivities)		
DESCRIPTION OF INTENDED USE OF DATA		
(e.g research, epidemiology, study, cost analysis of service, drug efficacy, disease surveillance)		
This data set will be used for a Mmed project.		
LIST WHO WILL HAVE ACCESS TO THIS DATA		
Dr Mike Levin (Department of Paediatrics, Somerset Hospital) Dr JA Simpson (NHLS, Greenpoint) Dr Andrew Whitelaw (Microbiology, GSH) Dr Kim Bonorchis (NHLS, Greenpoint) Dr Susan Meiring (Germs SA) Dr Karla Thomas (Paediatrics registrar, Somerset hospital) Henri Cararra (Biosatitician, UCT)		
DATA DETAILS		

Request Type	<input checked="" type="checkbox"/> New	<input type="checkbox"/> Modify	Data format	<input checked="" type="checkbox"/> Excel	<input type="checkbox"/> CSV
Frequency of Extract	<input checked="" type="checkbox"/> Once	<input type="checkbox"/> Repeat	If repeat, specify frequency	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly	<input type="checkbox"/> Monthly <input type="checkbox"/> Annually
Data Delivery	<input checked="" type="checkbox"/> E-mail	<input type="checkbox"/> CD/DVD			

University of Cape Town

INSTRUCTIONS TO AUTHORS

Please note that the journal now encourages authors to complete their copyright licence to publish form online

All manuscripts must be submitted online. Once you have prepared your manuscript according to the instructions below please visit the online submission web site. Instructions on submitting your manuscript online can be viewed [here](#).

The *International Journal of Epidemiology* is produced six times a year and publishes original work, reviews, articles of interest and letters in the fields of research and teaching epidemiology.

All submissions must be in the English language.

It is a condition of publication in the *Journal* that authors grant an exclusive licence to the International Epidemiological Association. This ensures that requests from third parties to reproduce articles are handled efficiently and consistently and will also allow the article to be as widely disseminated as possible. As part of the licence agreement, authors may use their own material in other publications provided that the *Journal* is acknowledged as the original place of publication and Oxford University Press as the Publisher.

Upon receipt of accepted manuscripts at Oxford Journals authors will be invited to complete an online copyright licence to publish form.

Please note that by submitting an article for publication you confirm that you are the corresponding/submitting author and that Oxford University Press ("OUP") may retain your email address for the purpose of communicating with you about the article. You agree to notify OUP immediately if your details change. If your article is accepted for publication OUP will contact you using the email address you have used in the registration process. Please note that OUP does not retain copies of rejected articles

Articles are accepted for publication on condition that they are contributed solely to the *International Journal of Epidemiology*. The editors cannot enter into correspondence about papers considered unsuitable for publication and their decision is final. Neither the editors nor the publishers accept responsibility for the views and statements of authors expressed in their contributions.

Manuscripts should be prepared in the Vancouver Style (see e.g. *Br Med J* 1979; **1**: 532-35) and **submitted online [here](#)**. They should not normally exceed 3000 words but review articles may be twice this length. Letters intended for publication should be marked 'For Publication'. Books and monographs for review should also be sent to the Editor.

Manuscripts should be double spaced with margins of 2.5cm. All pages should be numbered. Italics should be indicated by single underlining. Numbers followed by a unit should be written as figures as should all numbers above nine. Figures should not be used to start a sentence and those between 999 and 9999 should not be separated by spaces or commas while those over 10 000 should have a space after the thousand. Per cent should be written as % throughout. Full points should not be used after initials or contractions: J Jones, FRCS, 17 g, dl, Dr, etc. All measures should be reported in SI units followed, in the text, by traditional units in parentheses. For general guidance on the International System of Units and some useful conversion factors, see 'The SI for the Health Professions' (WHO, 1977). There are two exceptions: blood pressure should be expressed in mm Hg and haemoglobin as g/dl.

If the data are appropriate, age grouping should be mid-decade to mid-decade or in five-year age groups (e.g. 35-44 or 35-39, 40-44, etc, but not 20-29, 30-39 or other groupings).

TITLES

Titles should be short and specific. Subtitles may be used to amplify the main title.

AFFILIATIONS

The affiliations of each author must be given. If an author's present affiliation is different from that under which the work was done, both should be given.

SUMMARY

The summary should be no more than 250 words and consist of four sections labelled Background, Methods, Results and Conclusions. They should briefly describe the problem being addressed in the

study, how the study was performed, the salient results and what conclusions can be made from the results. Three to ten keywords should be added to the end of the Summary.

FUNDING

The following rules should be followed:

The sentence should begin: 'This work was supported by ...'

The full official funding agency name should be given, i.e. 'the National Cancer Institute at the National Institutes of Health' or simply 'National Institutes of Health' not 'NCI' (one of the 27 subinstitutions) or 'NCI at NIH' - see [the full RIN-approved list of UK funding agencies](#) for details

Grant numbers should be complete and accurate and provided in brackets as follows: '[grant number ABX CDXXXXXX]'

Multiple grant numbers should be separated by a comma as follows: '[grant numbers ABX CDXXXXXX, EFX GHXXXXXX]'

Agencies should be separated by a semi-colon (plus 'and' before the last funding agency)

Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author initials]'

An example is given here: 'This work was supported by the National Institutes of Health [P50 CA098252 and CA118790 to R.B.S.R.] and the Alcohol & Education Research Council [HFY GR667789].

Oxford Journals will deposit all NIH-funded articles in PubMed Central. See [Depositing articles in repositories – information for authors](#) for details. Authors must ensure that manuscripts are clearly indicated as NIH-funded using the guidelines above.

REFERENCES

Authors are responsible for the accuracy and completeness of reference lists. References in Vancouver Style should be in the order they appear in the text and numbered accordingly. These numbers should be inserted above the line whenever a reference is cited (...confirmed by other studies **23**). Numbered references should appear at the end of the article and should consist of the surnames and initials of all authors when six or less, when seven or more list just three and add *et al.*, title of article, name of journal abbreviated according to *Index Medicus* style, year, volume, first and last page numbers,

e.g. Bull Q, Doe J. Epidemiology and public health. *Int J Epidemiol* 1970; **5**: 702-10.

Titles of books should be followed by the place of publication, the publisher, and the year. 'Unpublished Observations', 'Personal Communications' and submitted manuscripts may not be used as reference but should appear in the text. Manuscripts in press may be cited in the references and details added on proof if possible.

ABBREVIATIONS

Words to be abbreviated should be spelt out in full the first time they appear in the text with the abbreviations in brackets. Thereafter the abbreviation should be used.

TABLES

Tables should be numbered consecutively in arabic numerals and should be kept separate from the text. Particular care should be taken to make tables self-explanatory with adequate headings and footnotes. The position of each table in the text should be indicated (Table 1 here).

FIGURES

Illustrations should be numbered, given suitable legends. They should be kept separate from the text. Colour illustrations can be reproduced if there is sufficient scientific merit in doing so. Authors will be expected to pay for the cost of colour origination in the print version of the Journal (£350/figure). Alternatively, black and white figures can appear in the printed version of an article with colour versions appearing online (for which there is no charge). Please state your preferred option (i.e. agreement to pay £350/figure for print and online colour or preference for online-only colour with no charge) upon submission via the online submission system.

Please ensure that the prepared electronic image files print at a legible size and are of a high quality for publication. For useful information on preparing your figures for publication, go to <http://cpc.cadmus.com/da>. You can also see our [figure guidelines](#).

APPENDICES

As a general rule, material of this nature should be incorporated in the text but separate sections can be published after the main text.

SPECIAL NOTES FOR STATISTICAL PAPERS

The correct preparation of statistical manuscripts is particularly important and the precise nature and position of each symbol must be clear. Complex formulae should be drawn out on a separate sheet and attached to the text at the appropriate place. In general, distinction should be made between:

- a. capitals and small letters;
- b. ordinary and bold-faced letters;
- c. certain greek letters and similar roman letters;
- d. subscripts, superscripts and 'ordinary' symbols.

Bold-faced symbols should be underlined with a wiggly line in pencil. Statistical symbols are automatically set in italics and need not be underlined except to prevent ambiguity, e.g. when an isolated letter, such as *a*, occurs in the text. Symbols should not be used to start a sentence.

COHORT PROFILES

Purpose: The ultimate aim of the IJE's cohort profile series is to provide up-to-date details of cohort studies across the world. Each profile should include key information about a particular cohort used in epidemiological studies. Cohort profiles should provide IJE readers with sufficient detail to enable them to; form collaborations, learn from each other and maximise use of existing resources.

Word count: Around 2500-3000 (should be succinct and indicative rather than exhaustive)

Eligibility: To be eligible for publication a cohort profile MUST:

1. Have collected and completed some analyses on at least one, baseline, round of data, so that some results in addition to baseline descriptive statistics can be presented in the profile.
2. Describe a study that has either completed prospective follow-up of participants or has funding and clear plans to do so.

In addition to these requirements, the IJE will give preference to cohorts with over 1000 participants at baseline and to cohorts for which follow-up data have been collected specifically for the cohort rather than just from routine data sources.

The IJE will accept profiles that describe cohort consortia. Such profiles should focus on the added value of the consortium rather than piecemeal descriptions of the constituent cohorts. Updates of cohort profiles already published will be considered in cases where the focus of the research, or the data collected have changed significantly. Please note that updated cohort profiles will ONLY be considered for publication online.

From December 2012 the IJE will have a regular Data Resource Profile series. This series will cover any dataset of use to epidemiologists that falls outside the rubric of a cohort study. Typical examples of data resources include the Indian National Family Health Survey Study; UK General Practice Research Database (GPRD), Indonesian Family Life Survey, and Korean NHANES. However, large randomised controlled trials and clinical case series with long-term follow-up will also generally be considered data resources rather than cohorts.

Format

Each profile is required to follow a similar format, using the subheadings:

Title and Author List: Your title should start with 'Cohort Profile' followed by the cohort name in full (acronyms in parenthesis). A maximum of 12 authors will be listed under the title. Additional authors and their affiliations should be included under the sub-heading 'Author list continued' at the end of the document.

Summary: A short free form summary (150 – 200 words) should describe why the cohort was set up, cohort participants, data collection phases, main categories of data, and data access. For every cohort profile accepted for publication this will appear in the print version of the IJE. Please note that the Summary should be included in the main text document submitted to Manuscript Central.

Key Messages A 'Key messages' box should be included in every cohort profile. It should not reiterate information that is already in the Summary, but in 3-4 short bullet points it should summarise the main

contributions of the cohort in terms of scientific findings.

The Summary and Key Messages of every cohort profile accepted for publication will appear in the print version of the IJE. However, as the full version of some profiles will only be published online it is vital that the Summary and Key Messages together should provide a succinct, stand alone mini-profile of the study.

Why was the cohort set up? What was the rationale for setting up the cohort including the original research questions it was set up to address? Where is it located and how is it funded?

Who is in the cohort? Describe the study design; the methods used to recruit participants; numbers invited and numbers who entered the study (give response proportion); and differences between responders and non-responders at baseline (ideally as a table of socio-demographic characteristics comparing responders to non-responders or responders to the general population from which the responders came).

How often have they been followed up? Provide details of how often questionnaires / examinations have been conducted.

In addition to response at baseline, loss to follow-up over time must be described, with summary statistics presented in a table or figure. A description of how those lost to follow-up differ from those remaining in the cohort should be provided as well as the results of any work completed to describe missing data. This section must be sufficiently detailed to provide readers with a clear picture over time of the population represented by the cohort.

Please note that this section should be omitted if no follow-up data have yet been collected.

What has been measured?

Give broad categories for each follow-up phase, e.g.

Phase	Measurements
Baseline 1935-40	Fasting blood samples taken, DNA extracted, fasting glucose, lipids, insulin assayed, serum aliquots stored at -80OC Self-reported socio-economic position Anthropometric measures: weight, height, waist & hip circumference Blood pressure Self-reported major behavioural CVD risk factors
Follow-up 1950	Questionnaire only: Self-reported major diseases and treatment Self-reported socio-economic position and behaviours
Ongoing	All participants are flagged with routine data sources providing deaths since baseline and cancer registry entries since 1980

Provide descriptions of unusual measurements (e.g. specialised scans; unique assays) and/or measurements that have been undertaken in sub-groups of the cohort.

This section should describe any linkages to morbidity, mortality and other routine data sources.

What has it found? Key findings and publications This should not be an exhaustive list, but an indicative summary of the most important findings generated by the cohort. If there is a web-page with a complete list of publications please note this and supply the web-address. The *IJE* strongly encourages authors to illustrate one or two of their main findings with a table or figure, in addition to describing the findings in the text. Please note it is expected that descriptions of key findings, albeit brief, will inform the reader what has been found rather what has been examined.

What are the main strengths and weaknesses? Please make sure both strengths and weaknesses are covered. It may be useful to readers setting up new cohorts to state briefly what you would do differently if you could start again and anything you regret leaving out. You may also comment on

anything you feel is particularly valuable but might not be possible today because of data protection or other difficulties.

Can I get hold of the data? Where can I find out more? The purpose of cohort profiles is to foster collaboration and maximise use of existing data. If the data are open access a web address must be provided. If an application is required to access the data, indicate where the application form can be found and the process for submitting an application. If access to the data is more limited please describe opportunities for collaboration. In all cases the name and contact details of a researcher to whom enquiries and queries can be submitted must be provided.

Please avoid using jargon and non-standard abbreviations.

Please note that the full version of most cohort profiles submitted after the 1st October 2012 will only be published online. Authors are reminded that both in terms of scientific merit and impact factor attribution, online only publication is regarded as no different from publication in the print version of the journal. Cohort profiles to be published in print as well as online will be selected by the Editors-in-chief.

DATA RESOURCE PROFILE SERIES

Review process: Data Resource Profiles (DRP) of potential interest to the IJE will be sent to the DRP handling editor. S/he will either review the submission or forward to an appropriate Editor who will seek external reviews, if required. Editors and external reviewers will be sent this set of instructions and asked to review the DRP against these.

What are we looking for?: For this *IJE* section, a DRP is defined as a collection of phenotypic data (with or without genotypic data) relevant to human health obtained from a defined population that is made available to bona fide researchers for the purposes of epidemiological, demographic, social and other related analyses. A DRP may be globally, regionally, nationally or sub-nationally representative and may be a single cross-sectional survey, repeated cross-sectional surveys; or large scale randomized or quasi-randomized evaluation studies with follow up for clinical events or changes in risk factors. Examples of DRPs that would be considered include the Indian National Family Health Survey Study; UK General Practice Research Database (GPRD), Indonesian Family Life Survey, Korean NHANES.

Purpose: The ultimate aim of the *IJE's* Data Resource Profile (DRP) series is to provide up-to-date details of data resources across the world. Each profile should include key information about a particular data resource that is currently in use or could be of use to epidemiological studies. Each profile should provide readers with sufficient detail to enable them to understand the scope of the data resource and how to access and make best use of the data.

Word count: around 2500-3000 (should be succinct and indicative rather than exhaustive)

Eligibility: To be eligible for publication in the DRP profile series, a DRP must:

- Describe a data resource to which data access is either open via a website or for which the author(s) or their institution have the right to grant at least collaborative access via a straightforward and transparent application process.
- Have completed collection and have made available at least one wave of data.

Format

Each profile is required to follow a similar format, using the subheadings:

Title and Author List: Your title should start with 'Data Resource Profile:' followed by the name in full followed by any acronym in parenthesis. A maximum of 12 authors will be listed under the title. Additional authors and their affiliations should be included under the sub-heading 'Author list continued' at the end of the document.

Summary: A short free form summary (150 – 200 words) should outline the area, units or groups and/or individuals covered by the data resource, data collection methods, main categories of data, and data access including either a web address or email address for data access enquiries or applications. Please note that the Summary should be included in the main text document submitted to Manuscript Central.

Key Messages: A 'Key messages' box should be included in every DRP. In 3-4 short bullet points it should summarise the unique features of the data resource. Key messages may include scientific findings and should not repeat material already included in the Summary.

Please note that the Summary and Key Messages of every DRP accepted for publication will appear in the print version of the IJE. However, the full version of some DRPs will only be published online. For

this reason please ensure that your Summary and Key Messages together provide a comprehensive mini-profile of the data resource.

Data Resource Basics: Brief details of the following information where relevant: Country or area covered by the data resource; Units, groups or individuals covered; Survey Type, (e.g. Demographic & Health Survey, Malaria Indicator Survey); Data collection dates and number of repeat surveys; Topic headings (e.g. diabetes testing, maternal mortality); and Funding sources. Some of this material might be best presented in tabular form.

Data resource area and population coverage: Where relevant, this section should include a map or series of maps that indicate the area covered by the data resource and major centres of data collection, e.g. hospitals. It must describe the units, groups and individuals from whom data are collected and describe how contact at each level was achieved and maintained (if relevant).

Survey frequency: The date of the survey and the number of units, groups and/or individuals surveyed should be provided. If repeat surveys have been carried out, the dates of each survey should be provided together with the numbers surveyed. Where appropriate these details should include numbers invited, the response rate and how well the sample represents the population from which it was taken. This information can be presented in tabular form. For recent or ongoing repeat surveys include the dates when data will be available.

Measures: The measures collected at each of the different levels included in the data resource, e.g. individual, household, group, should be described in as much detail as necessary i.e. methods for commonly used measures will not need to be described. At least partial presentation in tabular form is encouraged. This section should indicate the source (e.g. questionnaire, clinic exam, data linkage), type of data collected (e.g. biomarker, geographical, genetic, demographic), the methods used to collect the data, and the frequency. This section must be sufficiently detailed to provide readers with a clear picture of the data available

Data Resource use: This section should provide one or two brief illustrative examples of how the data resource can be used or examples of published work which has used this database. If you are aware of any ongoing specific data analysis plans please indicate these here to avoid duplication of effort by others interested in the data resource. Please also provide an up-to-date citation list for work published on the data resource.

Strengths and weaknesses: This section should include both the strengths and the limitations of the data. If the data resource is one of a series e.g. a Key Indicators Survey, please describe any features that are unique to the particular data resource or country/area location, if applicable.

Data Resource access: This section should describe how readers can access and download the data. The location and format of the data should be described together with variable lists and data dictionaries, where available. If the data are open access a web address should be provided. If an application is required, please indicate where the application form can be found and the process for submitting an application. Briefly indicate the software required to access the database and/or use the data, if applicable.

Please avoid using jargon and non-standard abbreviations.

LANGUAGE EDITING

Particularly if English is not your first language, before submitting your manuscript you may wish to have it edited for language. This is not a mandatory step, but may help to ensure that the academic content of your paper is fully understood by journal editors and reviewers. Language editing does not guarantee that your manuscript will be accepted for publication. If you would like information about one such service please click [here](#). There are other specialist language editing companies that offer similar services and you can also use any of these. Authors are liable for all costs associated with such services.

COPY EDITING

All accepted manuscripts are subject to copy editing.

PROOFS

The first author will receive a pdf proof of the article. Proof correction must not be used as an opportunity to revise the paper. Any essential changes should take up the same amount of space if possible. *Alterations, other than corrections of printer's errors, are expensive and may be charged to authors.* Corrections should be returned within in 3 days to guarantee inclusion.

It is particularly important to read reference lists at the proof stage in case any omissions/errors have been found and noted during copy editing.

The Editors reserve the right to make minor grammatical and other changes at any stage before publication. These are sometimes necessary to make the paper conform to the general style of the Journal. Proofs not returned to the Editorial Assistant within two weeks of the date of postmark may be held over to the next issue.

OFFPRINTS

Offprints may be purchased using the Oxford Journals Author Services site. Orders from the UK will be subject to a 20% VAT charge. For orders from elsewhere in the EU you or your institution should account for VAT by way of a reverse charge. Please provide us with your or your institution's VAT number.

SUPPLEMENTARY DATA

Supporting material that is not essential for inclusion in the full text of the manuscript, but would nevertheless benefit the reader, can be made available by the publisher as online-only content, linked to the online manuscript. The material should not be essential to understanding the conclusions of the paper, but should contain data that is additional or complementary and directly relevant to the article content. Such information might include more detailed Methods, extended data sets/data analysis, or additional figures (including colour). All text and figures must be provided in suitable electronic formats (for instructions for the preparation of Supplementary Data please go to [here](#)).

All material to be considered as Supplementary Data must be submitted at the same time as the main manuscript for peer review. It cannot be altered or replaced after the paper has been accepted for publication. Please indicate clearly the material intended as Supplementary Data upon submission. Also ensure that the Supplementary Data is referred to in the main manuscript where necessary.

University of Cape

Acknowledgements and Contributions:

Dr KM Thomas: Paediatric registrar, School of child and adolescent health, University of Cape Town: Formulated the topic and protocol, obtained, cleaned and analysed the data; wrote the manuscript.

Prof M Levin: Head of Allergy Services; Red Cross Children's War Memorial Hospital, Cape Town: Supervised the inception and completion of the protocol and manuscript.

Mr H Carrara: Biostatistician; University of Cape Town: Gave invaluable advice on the statistical analyses.

Dr JA Simpson: Microbiologist; NHLS Greenpoint: Helped with obtaining the data.

University of Cape Town