A century of South African battles against the pneumococcus –'the captain of death'

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A hundred years ago, Sir William Osler described the pneumococcus as the 'Captain of the men of death', referring to John Bunyuan's phrase in his book 'The life and death of Mr Badman', written more than 200 years earlier: "Yet the captain of all these men of death that came against him to take him away was the consumption, for it was that that brought him down to the grave". For Osler the captain of the men of death was not 'consumption' (tuberculosis) but pneumonia or the pneumococcus. During his time, acute pneumonia was responsible for more deaths than tuberculosis and the pneumococcus killed adolescents and young adults in the prime of their lives. Death followed a severe illness with high fever from 105°F to 107°F, fighting for air with rapid and shallow, often painful breathing. The condition escalated to a crisis, characterised by a sharp fall in temperature, and in many, death. Concerning those that recover Osler states, "Usually there is an abundant sweat and the patient sinks into a comfortable sleep" and "With the fall in the fever the respirations become reduced almost to normal, the pulse slows, and the patient passes from perhaps a state of extreme hazard and distress to one of safety and comfort". Osler also called the pneumococcus the 'friend of the aged' as it kills them gently without severe symptoms ("Taken off by it in an acute, short, not often painful illness, the old escape those 'cold gradations of decay' that make the last stage of all so distressing") and "one may say that to die of pneumonia is almost the natural end of old people". The advent of antibiotics in the 1940s dealt a severe blow to the captain's reign of terror and thanks to them the harshness of the escalating severity and crisis by death is now muted or rarely seen among young adults, at least in industrialised countries. It remains, however, a captain of the men of death among HIV-infected adults with limited access antiretroviral treatment and also among small children in the poorest countries without access to antibiotics. Small wonder the consternation then, when multiresistant strains emerged in South Africa in the 1970s.

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Introduction and background

A hundred years ago, Sir William Osler described the pneumococcus as the 'Captain of the men of death', referring to John Bunyuan's phrase in his book 'The life and death of Mr Badman', written more than 200 years earlier: "Yet the captain of all these men of death that came against him to take him away was the consumption, for it was that that brought him down to the grave". For Osler the captain of the men of death was not 'consumption' (tuberculosis) but pneumonia or the pneumococcus. During his time, acute pneumonia was responsible for more deaths than tuberculosis and the pneumococcus killed adolescents and young adults in the prime of their lives. Death followed a severe illness with high fever from 105°F to 107°F, fighting for air with rapid and shallow, often painful breathing. The condition escalated to a crisis, characterised by a sharp fall in temperature, and in many, death. Concerning those that recover Osler states, "Usually there is an abundant sweat and the patient sinks into a comfortable sleep" and "With the fall in the fever the respirations become reduced almost to normal, the pulse slows, and the patient passes from perhaps a state of extreme hazard and distress to one of safety and comfort". Osler also called the pneumococcus the 'friend of the aged' as it kills them gently without severe symptoms ("Taken off by it in an acute, short, not often painful illness, the old escape those 'cold gradations of decay' that make the last stage of all so distressing") and "one may say that to die of pneumonia is almost the natural end of old people". The advent of antibiotics in the 1940s dealt a severe blow to the captain's reign of terror and thanks to them the harshness of the escalating severity and crisis by death is now muted or rarely seen among young adults, at least in industrialised countries. It remains, however, a captain of the men of death among HIV-infected adults with limited access antiretroviral treatment and also among small children in the poorest countries without access to antibiotics. Small wonder the consternation then, when multiresistant strains emerged in South Africa in the 1970s.

South Africa has a rich history depicting the ravages of pneumonia and its prevention, notably in the gold mines during the early mining years and thereafter, dramatically, its role during the 1918 pandemic influenza. Similarly, medical scientists have been active in the fight against this and other microbial diseases in this country. The early history of pneumococcal vaccines was eruditely described by Robert Austrian in a Jeremiah Metzger lecture entitled 'Of gold and pneumococci' in 1977.[1] Because of the public health and financial consequences of pneumonia and other infectious diseases in South Africa and particularly in the mining industry, the South African government with a major input from the mining industry initiated steps which led to the establishment of the South African Institute for Medical Research (SAIMR) in 1912. The principal aim of this decision was to combat the scourge of infectious diseases in the country. Famous names which are linked to the early history of this fight in South Africa include General WCG Gorcas from the United States of America (USA) and Sir Almroth Wright from Britain.

Gorcas, who became Surgeon-General of the United States Army, was renowned for his role in ridding the Panama Canal Zone of yellow fever. He was invited to come to South Africa and he and his wife sailed to Cape Town in 1913 accompanied by Major RE Noble and Samuel T Darling. Earlier in 1905, Darling described the pathological features of three fatal cases of histoplasmosis from Martinique and Panama and named the causative organism *Histoplasma capsulatum* which he thought was a protozoon. During this visit, Gorcas recommended to the Transvaal Chamber of Mines the appointment of Dr AJ Orenstein to assist with the combating of infectious diseases in the mines. Orenstein gained international recognition for his indefatigable energy and drive in the institution of hygienic measures and proper housing with improved bed spacing in dormitories (sleeping compounds) in the mines. His incisive reports also resulted in the reconstruction of hospital wards and operating rooms, the appointment of full time mine medical officers, improved nursing services, better diets for miners, and the introduction of waterborne sewerage on all mines.[1]

Wright, who had been called the founder of modern vaccine therapy[2] and was almost as well known for his eccentricity as his scientific expertise,[1] conducted the first pneumococcal vaccine trial in the mines in 1911 with a vaccine which contained multiple local strains of pneumococci, the diversity of which had not been determined.. Dr Spencer Lister assisted with this trial and his involvement was the beginning of the illustrious career of Sir Spencer Lister who later became Director of the SAIMR and was knighted for his pioneer work on the development of polyvalent pneumococcal vaccines in South Africa.

The next doyen in the field of pneumococcal research who made a monumental contribution to the prevention of pneumococcal disease in South Africa, was Austrian from Philadelphia, USA, who conducted three large polyvalent pneumococcal polysaccharide vaccine trials in South African miners in the 1970s and was instrumental in the licensing in the USA of a polysaccharide pneumococcal vaccine with proven efficacy in adults. His pioneer studies made an international impact and will feature later in this article. More recently, Keith Klugman, now recognised internationally for his work and expertise on vaccine development, together with Shabir Madhi, newly appointed Professor in Vaccinology at the University of the Witwatersrand, conducted a large polyvalent pneumococcal conjugate vaccine trial in Soweto, South Africa, which showed good efficacy in young children including children infected with the HI virus. This study also deepened our understanding of the interaction between respiratory viruses, pneumococcal infections and *Mycobacterium tuberculosis* in children hospitalised for severe pneumonia.

The emergence of multiple antibiotic resistance in the pneumococcus, first described in Durban by Peter Appelbaum *et al* and by Michael Jacobs and colleagues in Johannesburg in the 1970s,[3,4] stimulated a spate of research involving clinical and epidemiological studies including surveillance programmes by South Africans involving Hendrik Koornhof, Roy Robins-Browne and Klugman. The clinical relevance of resistance was further explored in the context of both pneumonia and meningitis by Klugman and Ian Friedland in the early 1990s, contributing to international changes in the guidelines for the antimicrobial management of pneumococcal meningitis. .

Over the past two decades, pneumococcal disease has exponentially increased in South Africa, largely resulting from the spread of HIV infection. The role of HIV in expanding the burden of pneumococcal disease has been extensively studied among others by Charles Feldman, Professor of Pulmonary Medicine at University of the Witwatersrand, among adults and by Madhi in children. Additionally, a national pneumococcal surveillance programme established by Klugman in 2000,[5] which has since been greatly expanded to include active countrywide surveillance by Anne von Gottberg at the National Institute for Communicable Diseases, continues to provide valuable information as to the epidemiology of invasive pneumococcal disease and impact of HIV thereupon in South Africa. Feldman has also been at the fore of delineating the role of pneumolysin in pneumococcal disease and modulation thereof to improve the outcome of the treatment of pneumococcal pneumonia.

Early assessment of pneumonia in South African miners

At the turn of the 19th century, the average life expectancy in the Western world was less than 50 years and most of the early deaths were due to infectious diseases, mainly

gastroenteritis and respiratory diseases. These diseases affected all population groups but were much more common in infants and children, especially in the poor who lived under unhygienic and overcrowded conditions. At that time, infectious diseases were rife in South Africa and were of great concern to the mining industry where pneumonia was particularly prominent. In 1898, Brodie *et al* described the plight of 93 migrant mine workers who were recruited from Mozambique and arrived at a mine in midwinter.[6] After 14 days, only 16 of this group of miners were working because the others had become ill with respiratory tract infections, including pneumonia. Eight of the miners died. Among a larger group of 800 miners, autopsies were performed on 22 who died in the mine at the time. Specimens of lung tissue were taken for culture from 15 of these, and from seven encapsulated Gram-positive diplococci were isolated. These isolates were shown to be pathogenic to rabbits. From their studies, the authors concluded that of the illnesses they observed, the pneumococcus caused sinusitis, meningitis and pneumonia. In this report, the high attack rate for pneumonia among new recruits in winter was emphasised and prompted authorities to reconsider winter employment of new miners from tropical countries. In another mine (Premier Diamond Mine) a few years later, Nathan (1907) recorded an attack rate over an 18 months' period of eight/1,000 per month and a death rate of two/1,000 mines per month.[7]

In a prospective study of 8,000 immigrant miners, Maynard reported in 1913 that over 13% of new employees contracted pneumonia during their first six months in the mines.[8] The case fatality rate for pneumonia among miners was 39.2% with an incidence rate ranging from 300 to 500/100,000 between 1910 and 1912.[8] Comparable statistics gathered in Europe at that time revealed a mortality rate of 100-200/100,000 and a case fatality rate 17.4%.[9] By way of comparison, Maynard quoted an attack rate of 2.15% among recruits during their first year of service in a military garrison in Magdeburg, Germany.[8,9]

Early vaccine studies

The first vaccine trial initiated by Wright started in October 1911 and involved 50,000 participants used in six mass inoculation experiments.[10] These experiments differed in dosages and numbers of injections given, the mine sites where the studies were conducted and the proportions of control subjects used. The results of the studies were published in the *Lancet* in 1914 which concluded that "the comparative statistics which have been set forth above testify…. in every case to a reduction in the incidence-rate and death-rate of pneumonia in the inoculated".[10] He also stated that "the difference between the inoculated and the uninoculated is after a time effaced". He explained this finding on the basis of increasing immunity in the control subjects developed in the mines during the study period rather than waning of immunity in the inoculated.[10]

Dr George Maynard, statistician of the SAIMR, subjected the results of these trials to critical statistical analysis and concluded that the attack rate of pneumonia was lessened in the first four months following inoculation but that the vaccination had no significant effect on the case fatality rate.[1,8] Much later, Austrian, in his Jeremiah Metzger Lecture, commented, "The conclusions are not surprising when one considers that the number of pneumococcal types in the vaccine was unknown and may have been quite limited and that the doses of vaccine employed were, in the light of later knowledge, marginal at best".[1]

One of the first tasks of Lister of the newly founded SAIMR was to develop a pneumococcal vaccine incorporating pneumococcal capsular serotypes common in miners. He used the opsonisation and agglutination methods which he described in 1913 to type pneumococci isolated from sputum, and lung punctures of patients with pneumonia.[11] Although blood cultures were taken from patients with pneumonia in the Wright trials, they were not used in the subsequent trials conducted by Lister. The process of opsonisation involves specific enhancement of phagocytosis by neutrophils of pneumococcal capsular types or groups by antibody prepared against them. These serogroups, with a few antigenically related serotypes within serogroups, were later correlated with and incorporated into a typing scheme proposed by Cooper and associates.[12] Lund subsequently developed a system for typing serotypes that became known as the Danish scheme,[13] and in 1944 Eddy formulated the less commonly used American typing scheme.[14] Lister originally classified his pneumococcal strains into four groups: A, B, C and D, of which the first two were the most common. His work was published in 1913, three months after Dochez and Gillespie had described independently their pneumococcal groups I, II and III.[15]

In July 1914, Maynard started the first trial based on Lister's typing scheme.[16] Although not stated in the original report, according to a subsequent publication, five of Lister's serotypes were used, each administered in a dose of ~ two billion organisms.[17] The study population comprised 55,900 miners, half of whom received the vaccine and half of whom were used as controls. There was a 20% reduction of clinically diagnosed pneumonia in the vaccinated group ($p<0.0002$). Unfortunately bacteriological studies were not done to demonstrate reduction in illness caused by types in the vaccine.

A controversy which continued over the next two decades concerned the appropriate choice of control subjects.[1] Lister wrote in 1916, "In the system hitherto employed on the Rand for assaying the results of prophylactic inoculation against the Pneumococcus, a certain advantage conferred upon the uninoculated has, I think, been overlooked. If Pneumonia is spread, as I believe it to be, either directly from case to case or through the agency of carriers, it follows that the inoculation of half the inhabitants of a Native compound may interrupt the chain, not only of actual pneumonic patients, but also

of carriers. If the inoculation achieves this, it is obvious that the uninoculated half of the population will achieve an advantage which is not allowed for in the calculations".[18] This very valid argument induced Lister to conduct vaccination in specific mines and use other mines whose miners have not been inoculated for control purposes. In a landmark study conducted at an Army Air Force Technical School in the USA during World War II, MacLeod *et al* addressed this aspect in a carefully designed and meticulously executed study.[19] Following surveillance of pneumococcal serotypes responsible for pneumonia during the two winter seasons before introduction of the immunisation phase of the trial, six serotypes responsible for 75% of 1,500 pneumonia cases were identified and the four most common serotypes were administered to vaccinees while the other two less common serotypes served as controls. In a randomised allocation of vaccine, 3,755 men received the polyvalent preparation and 3,975 received a saline control injection.

The other important problem with the Lister and Ordman studies, concerning standardisation of the polysaccharide antigens, was solved through the use of purified polysaccharides of established immunogenic potency prepared by Heidelberger who was one of the authors of the publication describing the MacLeod vaccine study.[19] This study clearly showed that the vaccine produced type-specific immunity which appeared within a period of two weeks and lasted for a minimum of six months. They also showed that immunisation of alternate subjects in the study population reduced greatly the incidence of pneumonia in the non-immunised and that the carrier rate for the vaccine serotypes was lowered significantly in the immunised group compared with controls

Several vaccine trials similar to Maynard's 1914 study were conducted during the next few years in the mines with variable results. According to Austrian, the most convincing evidence of efficacy was the findings of the Crown mines trial in 1915.[1,20] Of 82 consecutive cases of lobar pneumonia investigated bacteriologically in this study, there was not a single case associated with a vaccine type whereas in the absence of controls Lister extrapolated from epidemiological data that there should have been 120 had the vaccine not been received.[20] Studies of immunisation in South Africa prior to 1931 were critically reviewed by Orenstein who concluded that that in only one instance the results "appeared to justify the adoption of prophylactic vaccination".[17]

Apart from his vaccine studies, Lister conducted many experiments in animals on the immunogenicity of pneumococcal serotypes. He demonstrated opsonins and agglutinins in the serum of animals and in immunised men and based on such assays he demonstrated that "larger doses than 1,000 million, even of a single strain of Pneumococcus, are necessary in order to give rise to demonstrable antibodies".[18] As a result of Lister's studies, it was decided in 1918 to vaccinate all new recruits with an octavalent vaccine containing eight whole bacterial cells of Lister's groups A, B, C, E, G, H, J and K.[21] In 1920, Lister was knighted for his work on the immunology of the pneumococcus. Many years later, Austrian commenting on Lister's sudden death in 1939 in his published Jeremiah Metzger Lecture, said "His sudden death in 1939 while Director of the South African Institute for Medical Research deprived that country of its most distinguished medical scientist".[1]

Ordman became involved in vaccine studies in the early 1930s and he and Lister extended the range of antigens to include additional pneumococcal serotypes as well as other bacterial species including using current nomenclature, *Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae* and *Moraxella catarrhalis* species.[22] Reviewing the studies of Lister and Ordman between 1931 and 1934, MacLeod *et al,* referring to Heffron's review of antipneumococcal immunisation in his book on pneumonia and the pneumococcus published in 1939,[9] suggest that the Lister and Ordman studies demonstrated that "immunization with a polyvalent pneumococal vaccine reduces the incidence of pneumonia caused by the same pneumococcal types".[19] Pneumococci of types I, II, III, V, VII, XII and XIV were represented in the vaccine, 1cc, containing 1,000 million organisms of each type, except for type II of which 2,000 million per cc were included. "The best results were obtained in the prevention of pneumonia caused by type II. In the control group 27.9% of the cases were caused by type II whereas in the vaccinated group this was reduced to 4.0%. With the other types represented in the vaccine a beneficial effect was also observed, but in no instance as good as with type II. In prior studies of Lister and Ordman, the prophylactic value of anti-pneumococcal immunization appeared to be less definite".[19]

The Austrian era

In the early 1970s, researchers in the USA were looking for populations in which to test contemporary vaccines. Professor James Gear, son-in-law of Sir Spencer Lister and Director of the SAIMR at the time, while on sabbatical at Harvard University advised Prof Robert Austrian from the Department of Research Medicine, University of Pennsylvania School of Medicine, that pneumonia was still very common in South African mines. Gear facilitated a visit for Austrian to meet senior mine medical officers to determine the feasibility of conducting vaccine trials in miners in this country. Professor Hendrik Koornhof, then newly appointed head of the Department of Medical Microbiology of the SAIMR and the University of the Witwatersrand, visited Austrian in 1970 during which the prospects of conducting a vaccine study in a South African mine(s) were discussed. Following the visit, a two-year pre-trial clinical and bacteriological surveillance study was instituted prior to the start of three large vaccine studies under Austrian's leadership. This survey established an attack rate of 100 per 1,000 of pneumonia of radiologically confirmed pneumonia in men coming to work for the first time with many bacteraemic cases confirmed as

pneumococcal on blood culture.[22] Serotyping was performed using the capsular swelling method by Mr Stan Hayden-Smith and Mrs Valerie Kuhnle at the SAIMR in Johannesburg and cultures were subsequently sent to Austrian for confirmation at his pneumococcal typing laboratory and future reference. To prepare him for the laboratory requirements of the studies, Austrian arranged for Hayden-Smith to visit the Staten Serum Institute in Copenhagen, Denmark, to get first hand experience in pneumococcal typing and in the process obtain a few antisera for typing of rare serotypes. Hayden Smith also visited Gerald Schiffman's laboratory at Downstate Medical Center, State University of New York, to gain experience in the performance of a radioimmunoassay for the measurement of pneumococcal capsular antigens and antibodies to these antigens. As part of the forthcoming studies, serological tests were performed at the SAIMR and in Schiffman's laboratory to measure antibodies in acute and convalescent sera to serotypes isolated from patients.

Between 1971 and 1977, three large blinded randomised controlled trials were conducted at the East Rand Proprietary Mine (ERPM) involving 12,000 newly recruited miners.[22] In all three trials, random numbers were used to assign to three groups of miners, namely 50 µg each of the polysaccharide antigens to the pneumococcal vaccine group or 50 µg of group A meningococcal vaccine as a first control group or a saline placebo injection to a second control group. In the first trial, involving 4,497 miners, a hexavalent vaccine containing serotypes 1, 3, 4, 7, 8,and 12 polysaccharide antigens and in the two subsequent trials a tridecavalent vaccine containing the same six serotypes plus serotypes 2, 6, 9, 14, 18, 19 and 25 were used. Vaccine efficacy was assessed according to protection afforded by the tridecavalent vaccine in patients with a) bacteraemic pneumococcal pneumonia and b) those with putative pneumococcal pneumonia and/or pneumococcal bacteraemia associated with capsular types in the vaccine and c) radiologically confirmed cases, irrespective of cause. In all three assessments, protection was determined on episodes occurring later than two weeks of having received the vaccine trial components. Highly significant efficacy was achieved in the bacteraemic cases while in the radiologically confirmed cases of pneumonia, irrespective of cause, significant protection was also demonstrated. An overall vaccine efficacy of 78.5% was achieved in the bacteraemic plus radiologically confirmed cases. Excellent type-specific immunity was demonstrated amongst the common serotypes encountered; viz types 1, 2, 7, 8, 12 and 25. An interesting finding was that of the 10 bacteraemic cases caused by serotypes represented in the vaccine, eight were caused by serotype 1. It was subsequently found that type 1 vials contained 9 µg rather than the correct 50 µg dose.[22]

A similar study conducted at the same time at the Kloof mine only differed from the Austrian studies in that one control group received a combined meningococcal group A and C vaccine and the serotypes present in the vaccines differed slightly.[23] The vaccine was manufactured by the Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania, USA. The hexavalent vaccine used by them contained pneumococcal serotypes 1, 2, 4, 8, 12 and 25 and the dodecavalent vaccine serotypes 1, 2, 3, 4, 6, 8, 9, 12, 25, 51, 56 and 73. In these studies, 1,523 persons received the pneumococcal vaccine and 3,171 were given control preparations. The hexavalent vaccine provided a 76% reduction in cases caused by homologous serotypes and there was a 92% reduction in the cases afforded the 12-valent vaccine.

Surveillance of antimicrobial resistance: 1979-1991

Soon after multiply-resistant *Streptococcus pneumoniae* isolates were discovered in Durban and Johannesburg,[3,4] a national surveillance programme for antimicrobial resistance in pneumococci isolated from blood and cerebrospinal fluid specimens was initiated at all the major teaching hospitals in South Africa, excluding the University of Natal (now the University of KwaZulu-Natal). This important national survey was initiated and facilitated by Dr Eric Glatthaar, then deputy director of the Division of Infectious Diseases of the national Department of Health, and throughout the survey period pneumococcal typing and antibiotic susceptible findings were submitted to the Department of Health. These data were subsequently analysed and recorded in a comprehensive departmental document by Dr John Frean (presently head of the Special Bacterial Pathogens Unit of the National Institute for Communicable Diseases, and Associate Professor in Microbiology at the University of the Witwatersrand) in Dr Hans Kustner's statistics section of the department. Systemic isolates were submitted to the central SAIMR laboratories for susceptibility testing, which included minimum inhibitory concentration determinations as described by Jacobs *et al*;[24,25] this method was subsequently modified according to the specifications of the National Committee for Clinical Laboratory Standards. All cultures were initially screened for penicillin resistance (with use of 1 µg oxacillin discs), tetracycline, chloramphenicol, erythromycin, cotrimoxazole and rifampicin. A comprehensive report of the national surveillance findings for the period 1979-1986 was compiled by Klugman and Koornhof in 1988.[26] Surveillance continued into the 1990s and was subsequently extended by Klugman to include *Neisseria meningitidis* and *Haemophilus influenzae* as an important activity of the Respiratory and Meningeal Reference Unit of the University of the Witwatersrand and the Medical Research Council of South Africa.[5]

During the 12-year surveillance period of 1979 to 1990, the prevalence of penicillin resistance increased from 4.9% to a peak of 16.3% in 1989.[27] Other prevalence rates for

4,597 isolates tested during the years 1987-1990 were: high-level penicillin resistance (MICs >1 µg/mL), 2.3%; multiple drug resistance, 1.0%; tetracycline resistance 5.2%; erythromycin resistance 2.3% and rifampicin resistance 1.6%. Cotrimoxazole resistance increased from 32% in 1985 to 44% in 1991. The most common penicillin-resistant serotypes during the period 1979-1986 were: 6A/6B 59%; *19A*/19F 26%; 14 13%; and *23F*/23B 0.4% (the predominant serotypes within serogroups 19 and 23 are indicated in italics). The corresponding figures for the period 1987-1990 were 45%, 26%, 21% and 8% with the prevalence of types 14 and 23F increasing sharply between these two periods.[27]

Early epidemiological studies related to nasopharyngeal carriage

Several studies on the prevalence and spread of antibiotic-resistant pneumococci since the discovery of high-level penicillin resistance in Durban and Johannesburg in 1977 have been conducted. In 1978, Dr Joel Ward, then associated with the Bacterial Diseases Division, Bureau of Epidemiology of the Centers for Disease Control, Atlanta, USA, visited South Africa to investigate epidemiological aspects of emerging antibiotic-resistant pneumococci. Several studies were conducted by Ward (CDC) in collaboration with the SAIMR, the University of Natal in Durban and the University of Cape Town.[28-30] It was clear that multiple-antibiotic and high-level penicillin resistance were prevalent in paediatric wards at King Edward VIII Hospital in Durban and Baragwanath Hospital (now the Chris Hani-Baragwanath Hospital) in Johannesburg and in two isolation hospitals serving these two academic hospitals.

Nasopharyngeal spread in paediatric wards

In an overcrowded ward in the Johannesburg isolation hospital where 76 patients with measles were being treated (71% of whom carried multiply-resistant pneumococci), nine of 10 newly admitted patients and all of 14 patients for whom initial cultures of nasopharyngeal specimens were negative for pneumococci carried multiply-resistant strains three days later, a finding that suggested an acquisition rate of 96%.[4] At another less crowded hospital, six (15%) of 39 children (non-carriers) were negative in the initial survey, but were positive three days later during a follow-up survey. These findings showed that children readily acquired resistant pneumococcal strains in the hospital and suggested that overcrowding enhanced the spread of such strains.

Effect of antibiotics on carriage

The significant role of prior administration of antibiotics in the carriage of resistant strains is illustrated in Table 1. These data show that the prior use of penicillin or chloramphenicol was associated with a significantly lower rate of carriage of pneumococci (p<0.0003); however, it resulted in a significantly higher rate of strains resistant to both penicillin and chloramphenicol (p<0.0005).[29]

Age-related carriage

Penicillin-resistant pneumococci were found to be significantly more common in nasopharyngeal carriers in children <4 years of age than in older children and adults. This was illustrated as an example in 1989-1990 where 41% of 362 isolates in children under 4 years of age were penicillin-resistant compared with 6% of 521 isolates from older age groups (p<0.000001). A similar trend was found with chloramphenicol (5.5% vs. 0.7% in the respective age groups; p<0.00001). Age-related differences were, however, not significant with respect to tetracycline or erythromycin resistance during this period.[27] Similar findings were reported from Durban by Robins-Browne *et al* in 1984.[31]

Prospective study in hospitalised children

New insights into the effect of hospitalisation and administration of β-lactam antibiotics on carriage of penicillin-resistant pneumococci were obtained in a prospective study conducted at Baragwanath Hospital in 1988 by Ms Ingrid van den Berg for a Masters degree dissertation. One hundred children under 10 years of age were monitored weekly for nasopharyngeal carriage of penicillin-resistant pneumococci during their stay in the hospital.[27,32] There were 53 carriers of pneumococci on admission, in 25 of whom the pathogen was eradicated while in hospital (20% of these carriers received β-lactam antibiotics); the organism persisted in the 28 other carriers, and 17 children acquired nasopharyngeal pneumococci in the hospital. Of the 74 children (43 carriers) who had not received antibiotics before admission, 45 (30 carriers) were given β-lactam antibiotics in the hospital. Only 10 of these children remained carriers after receiving β-lactam therapy, indicating significant reduction in the carriage rate for pneumococci (p<.0001). The overall effect of hospitalisation, including exposure to β-lactam antibiotics, on the carriage of penicillin-resistant pneumococcal strains is reflected in the carriage rate of penicillin-resistant strains

Table 1: Carriage of antibiotic-susceptible and antibiotic-resistant pneumococci in hospitalised children with or without prior antibiotic therapy in Durban

	Proportion of carriers (%)*	Proportion of carriers with resistant strains (%) †
With antibiotic therapy¶	87/322 (27)	60/87 (69)
Without antibiotic therapy	77/178 (43)	21/77 (40)

NOTE. Data are from Koornhof *et al*[30]
* p=.0003 (Fisher exact test).
† Received penicillin or chloramphenicol during the 30 days before the survey; p<.0005 (Fisher exact test).
¶These strains were resistant to penicillin and chloramphenicol

Table 2: Effect of hospitalisation on carriage of pneumococci among 100 South African children

	Distribution of pneumococci among carriers (%)			
Carriage status*	Total no of carriers	Penicillin-susceptible	Intermediately penicillin-resistant	High-level penicillin-resistant
On admission	53	29 (55)	17 (32)	7 (13)
Persistent	28	9 (32)	8 (29)	11 (39)
Acquired	17	3 (18)	5 (29)	9 (53)
On discharge	45	12 (27)	13 (29)	20 (44)

Note: Data are from Koornhof *et al* and Van Den Berg.[27,32] Of 53 carriers on admission, the organism was eradicated in 25, 20 of whom were receiving β-lactam therapy; 28 remained persistent carriers, Seventeen patients became carriers in the hospital, resulting in 45 carriers on discharge from the hospital. * Difference between carriage status on admission and on discharge; P=0.0003 (all penicillin-resistant strains), and p=.0001 (fully resistant strains).

Table 3: Association between the administration of β-lactam antibiotic therapy in hospital and carriage of pneumococci in 100 children admitted to Baragwanath Hospital, Johannesburg

	Distribution of carriers of indicated pneumococci								
	β-lactam therapy					No β-lactam therapy			
Carriage status	Total no of carriers	No of carriers (subtotal)	Susceptible	Intermediately penicillin resistant	High-level penicillin resistant	No of carriers (subtotal)	Susceptible	Intermediately penicillin resistant	High-level penicillin resistant
On admission	53§	37	20	11	6	16	9	6	1
Persistent	28	17	3	4	10 (6)†	11	6	4	1
Acquired	17	6	-	1	5 (9)‡	11	3	4	4
On discharge	45	23	3	5	15	22	9	8	5

Note: Data from Koornhof *et al.*[27] The effect of β -lactam antibiotics on carriage of all penicillin-resistant pneumococci is based on figures on discharge (p=.08) and carriage of fully resistant strain (p=.01).

§ Of the 53 carriers on admission, 10 received therapy before admission to the hospital. † Six children persisted in carrying high-level penicillin-resistant strains while an additional four children who carried less resistant strains on admission harboured high-level penicillin-resistant strains on discharge. ‡ Five children acquired high-level penicillin-resistant strains de novo while an additional four carriers of strains for which the MICs of penicillin were µg/mL became carriers of high-level penicillin-resistant strains.

on admission (24 [45%] of 53 patients) versus that on discharge (33 [73%] of 45) (p=.003). Similarly, acquisition and persistence of pneumococcal carriage in the hospital resulted in an increased prevalence of high-level penicillin resistance (p<.001; Table 2).

Data on the effect of β-lactam therapy on carriage of penicillin-resistant strains are summarised in Table 3. A large proportion of carriers harbored penicillin-resistant pneumococci on discharge, including those who received β-lactam antibiotics (20 [87%] of 23) and those who did not receive these drugs (13 [59%] of 22; p=.08). The difference in carriage rate of pneumococci with high-level penicillin resistance between the two groups was significant (p=.01).

The results of the studies described above clearly demonstrate important factors that play a role in the selection of penicillin resistance in the nasopharyngeal reservoir of young hospitalised children. These include the high carriage rates of penicillin-resistant strains among young children, the loss of pneumococcal strains susceptible to β-lactam antibiotics in some of these children while they are receiving these drugs, and the acquisition of strains that are mainly penicillin-resistant as a result of cross infection in the hospital in the presence or absence of antibiotic selection pressure. These factors resulted in a high proportion of carriers harbouring penicillin-resistant strains on discharge. Whether the resistant strains among the persistent carriers were acquired in the hospital or whether they were generated in the nasopharynx through mutation or transfer of genes from coexisting strains or species is not known.

Surveillance of pneumococcal disease in South Africa

Following the identification of multiply-resistant strains of pneumococci in hospitalised children in Durban and Soweto, Koornhof convinced the academic centres and SAIMR laboratories to send all invasive pneumococcal isolates to the SAIMR for typing and susceptibility testing. These data, from 1979 to 1986, were collated and reviewed in 1988.[26] and an analysis of 4,766 invasive pneumococcal disease (IPD) isolates revealed that resistance had increased to penicillin (using the breakpoint of 0.12 ug/ml) from 3.8% to 14.1% during this period. The great majority of penicillin-resistant strains (92%) belonged to serotype 14 or serogroups 6 and 19. Follow-up surveillance using the same database as 1990 was published in 1992.[27] Antimicrobial isolates from 1991 to 1998 with penicillin resistance at the intermediate breakpoint further increased to 18% and macrolide resistance emerged in both children and adults.[33]

A national laboratory-based surveillance system for IPD was introduced in South Africa in 1999 by Dr Robyn Huebner and colleagues.[5] Laboratories performing clinical microbiology diagnostic tests were requested to send reports of laboratory-confirmed IPD together with isolates to a central laboratory in Johannesburg. Basic demographic details such

as age, gender, date of specimen, and source of isolate were collected. In 2003, this system was enhanced to become an active surveillance system with frequent communications and provincial visits to increase case reporting, and regular audits to estimate the number of cases not reported routinely. In addition, for cases occurring at sentinel hospitals located in all nine provinces, expanded clinical and demographic information including admission date, human immunodeficiency virus (HIV) serological status, discharge diagnosis and outcome are collected. Cases are defined as patients with *Streptococcus pneumoniae* identified in normally sterile site specimens (eg. cerebrospinal fluid [CSF], blood, joint fluid). Using data from this surveillance system, it was possible to estimate the potential coverage of the polysaccharide protein conjugate pneumococcal vaccine by province and over several years, both the original 7-valent vaccine, and newer formulations such as the 10- and 13-valent vaccines. In 2006, the proportion of serotypes causing IPD included in 7-valent vaccine was 70% in infants <1 year, 74% for 10-valent vaccine and 83% for the 13-valent vaccine. In 2003, the first case of paediatric invasive disease due to levofloxacin-nonsusceptible *S. pneumoniae* detected in a child in a TB hospital was reported by Von Gottberg *et al*.[34] The emergence, spread and evolution of levofloxacin-nonsusceptible *S. pneumoniae* in two additional TB hospitals where fluoroquinolones were used to treat multidrug-resistant TB was described in 2008.[35,36] With the description of the 91st pneumocccal serotype, serotype 6C, Du Plessis and colleagues reported the prevalence of IPD due to serotype 6C in South Africa: overall prevalence was low during the period analysed (2005-2006), disease occurred predominantly in adults, more than one-half of the 6C isolates were from laboratory-confirmed meningitis and were fully susceptible to penicillin.[37] Additional recent work using isolates from this active laboratory-based surveillance has included the description of the predominant clone of serotype 3 causing IPD[38] and the molecular characterisation of macrolide-resistant pneumococci.[39]

Spread of resistant strains from hospitals into the community

The initial emergence of multiresistant pneumococci in South Africa was confined to nosocomial infections in hospitalised cases but follow-up of surveillance cases at the Baragwanath Hospital led Klugman and Koornhof to believe that apparently resistant infections were being acquired in the community. A series of community carriage studies were then performed which identified both novel patterns of multiple resistance excluding penicillin resistance,[40] but also high rates of carriage of these and of other penicillin-resistant pneumococci among children attending day care centres in Soweto and in periurban areas around Tzaneen in Mpumalanga.[41] The first documented case of community-acquired pneumonia due to penicillin-resistant pneumococci in South Africa, and probably in the world, was published in the *New England Journal of Medicine* in 1985 by Feldman *et al*.[42] By 1990, the spread of pneumococci resistant to antibiotics had been documented worldwide leading to a comprehensive global review of the problem.[43]

Mechanisms of resistance

During the 1990s, the Medical Research Council of South Africa awarded and supported the establishment of a Pneumococcal Diseases Research Unit to Klugman. Klugman, together with a succession of Doctorate students, discovered the molecular basis of resistance to a number of antimicrobials. These included a series of studies on penicillin binding proteins (PBPs) of wild type resistant strains, by Anthony Smith, the first of which was on PBP 2b;[44] the detection for the first time of *tet*(O) in the pneumococcus by Carol Widdowson;[45] the molecular basis of trimethoprim resistance;[46] Thanugarani Padayachee identified novel mutations associated with rifampicin resistance;[47] the acquisition of a transposon conferring chloramphenicol resistance in the pneumococcus from a staphylococcal plasmid;[48] Peter Adrian also described the molecular basis of evernimicin resistance;[49] Lesley McGee described the discovery of dual mechanisms of macrolide resistance, *erm* + *mef* in the pneumococcus;[50] and Nicole Wolter described the molecular basis of oxazolidonone and telithromycin resistance in the pneumococcus.[51,52]

Clinical relevance of resistance

South African researchers have been at the forefront of defining the clinical relevance of antimicrobial resistance in the pneumococcus. Initial work by Klugman and Ian Friedland showed that intermediate penicillin resistance led to clinical failure for pneumococcal meningitis.[53] These studies were followed up in clinical studies in South Africa to define the current treatment of choice for cephalosporin-resistant pneumococcal meningitis.[54] and the failure of cefuroxime for pneumonia in a large multicentre study including many South African patients in collaboration with Victor Yu of Pittsburg, USA.[55]

Pneumococcal pathogenesis

A number of South African researchers have been investigating various aspects of the pathogenesis of pneumococcal infection over a significant number of years. Many studies have addressed the potential role of pneumolysin, a thiol-activated, cytolytic, protein toxin thought by many to be one of the most important virulence factors of the pneumococcus. Initial work with this toxin was undertaken by Feldman during an Medical Research Council (SA)-supported post-doctoral scholarship in the Host Defence Unit, Department of Thoracic Medicine, Royal Brompton Hospital in the UK. These initial studies documented that pneumolysin slowed ciliary beating in human ciliated epithelium *in vitro*.[56] The research data suggested that this may be a strategy adopted by the pneumococcus to assist

in its colonisation of the airway. Further investigations also documented that pneumolysin itself had pro-inflammatory activity and in an experimental model of pneumonia, recombinant pneumolysin alone caused histological changes indistinguishable from that of pneumococcal infection of the rat lung *in vivo*.[57] This area of research work was continued by Feldman on his return to South Africa in collaboration with Professor Ronald Anderson of the University of Pretoria (MRC Unit for Inflammation and Immunity) and the various members of his research team. Additional studies addressed the activity of other toxin virulence factors of the pneumococcus, either alone or in combination with pneumolysin. One study investigated the effects of reactive oxidants on human ciliated epithelium *in vitro* since hydrogen peroxide had, at that time, been described as an additional virulence factor of the pneumococcus. In this study it was demonstrated that hydrogen peroxide also caused ciliary slowing, ultimately leading to complete ciliary stasis.[58] When the effects of hydrogen peroxide were studied in combination with pneumolysin, they were both found to have similar effects on ciliary function; furthermore, their actions were additive rather than synergistic and there was no evidence of any antagonism between the two toxins.[59] In contrast, hyaluronidase, another pneumococcal toxin, had no effects of its own on ciliary function but it did augment pneumolysin-induced injury to human ciliated epithelium.[60] Dr Riana Cockeran, working in Anderson's unit, completed her PhD with further studies on pneumolysin, investigating its interactions with host immune cells. She demonstrated that pneumolysin potentiated the pro-inflammatory activities of human neutrophils (increased superoxide production and elastase release) by its pore-forming mechanism, which resulted in calcium influx.[61] Furthermore, she demonstrated that pneumolysin activated NfκB and increased the synthesis and release of IL-8 by human neutrophils and also induced the generation of prostaglandin E_2 and leucotrine B_4.[61,62] The authors suggested that these interactions of pneumolysin with human neutrophils may exaggerate inflammatory responses in human infections.

Studies such as these appear to indicate that pneumolysin, a toxin produced by almost all clinically relevant pneumococci, may play a crucial role in colonisation, invasion and dissemination of the pneumococcus, as well as contribute to host tissue inflammation. Being a highly immunogenic polypeptide molecule, it has been suggested that pneumolysin may act as a suitable protein carrier for a polysaccharide conjugate vaccine, whereas in acute disease pharmacological strategies targeting pneumolysin, such as the use of macrolides in therapy, may be associated with improved outcomes. As such, a number of retrospective studies had indicated that combining a macrolide with standard ß-lactam therapy appeared to be associated with a better outcome in community-acquired pneumonia, including the subset of patients with pneumococcal bacteraemia. One study that came from the collaboration with Professor Victor Yu (described elsewhere) was the first prospective study (observational in design) that indicated that in severely ill patients with bacteraemic pneumococcal disease, combination therapy was associated with lower 14-day mortality.[63]

There remains considerable debate as to why adding a macrolide to standard ß-lactam therapy should be associated with a better outcome in patients with bacteraemic pneumococcal pneumonia. Anderson and his colleagues, in a series of studies, clearly indicated that macrolides and macrolide-like agents but not other antibiotics commonly used in the treatment of pneumonia (including aminopenicillins, cephalosporins, aminoglycosides and fluoroquinolones) in sub-MIC concentrations, and even in macrolide-resistant strains of pneumococci, caused significant attenuation of the production of pneumolysin.[64,65]

Pneumococcal community-acquired pneumonia in the setting of HIV infection

With the advent of the HIV epidemic, a large number of investigators in South Africa (including Crewe-Brown, Feldman, Jones, Karstaedt, Klugman and Madhi) studied the impact of HIV infection on the epidemiology, clinical features and outcome of invasive pneumococcal infections, particularly those associated with bacteraemic pneumonia and meningitis. These studies clearly demonstrated a substantially increased risk of IPD in HIV-infected adults and children.[66-71] For example, the overall burden of severe IPD was 41.7-fold increased in HIV-infected compared with HIV-uninfected children.[71] There was also a greater prevalence of isolates with reduced susceptibility to penicillin and co-trimoxazole, and even multiple drug resistance because of a heightened susceptibility of the children to infections with paediatric serogroups that more commonly carried resistance genes.[71,69] At that time, prior to the introduction of the newer conjugate pneumococcal vaccines, *Streptococcus pneumoniae* exceeded *Haemophilus influenzae* type b as the most common pathogen causing meningitis in children, and HIV-1-infected children had a higher mortality rate than uninfected children (30.6% versus 11.8%, respectively; p=0.01).[72]

Other studies confirmed the higher burden of pneumococcal disease in HIV-infected individuals and the increased prevalence of paediatric serogroups/types expressing antibiotic resistance, even among the adult cases.[67] Some of the initial studies suggested that this higher incidence of infections with paediatric serogroups/types harbouring antibiotic resistance genes was more common in women and this was confirmed in a study of 1,022 adults with either pneumococcal bacteraemia or meningitis and HIV infection sourced from databases that existed in Johannesburg.[73] Initial studies of bacteraemic pneumococcal pneumonia in adults confirmed many of these findings and also suggested that the mortality was not higher in HIV-infected adults.[74] However, a more recent international collaborative study,

which included South African investigators, when stratifying patients with bacteraemic pneumococcal pneumonia by age and severity of illness, clearly documented a higher mortality among HIV-infected cases, with a trend for increasing mortality as the CD4 cell count decreased.[75]

Guideline for the management of community-acquired pneumonia in South Africa

South Africa was one of the earliest countries to develop guidelines for the management of community-acquired pneumonia in adults. These were first published in 1996, and the third, and latest update, was published in 2007.[76] This process was initiated by Feldman, who has remained corresponding author, but the Working Group, which has evolved with each update, has had appropriate representation from around the country and others that have played a significant role include Koornhof and Klugman and, more recently, Dr Adrian Brink (Ampath National Laboratories, Johannesburg). Additionally, guidelines for management of pneumonia for HIV-infected and HIV-uninfected children were also developed in South Africa.[77]

Pneumococcal conjugate vaccine

Whereas the pneumococcal polysaccharide vaccines pioneered by Macleod and Austrian proved to be efficacious in preventing severe pneumococcal disease in adults and were subsequently developed to confer protection against 23 pneumococcal serotypes,[22,23,78,79] these vaccines were largely ineffective in children under 2 years of age who harboured the greatest burden of pneumococcal disease. Additionally, there was also conflicting reports of the efficacy of the pneumococcal polysaccharide vaccines in HIV-infected adults, with no efficacy being established in African studies.[80] Developing on the observations of improved immunogenicity of polysaccharide antigens when coupled to protein antigens and coupled with the success of polysaccharide-protein conjugate vaccine in preventing invasive *Haemophilus influenzae* type b disease in children,[81] a polysaccharide-protein conjugate vaccine composed of seven and nine serotypes was developed by Wyeth (USA) and underwent clinical trials in United States (7-valent vaccine containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) from 1995,[82] in South Africa from 1996 and subsequently in The Gambia (9-valent formulation including serotypes 1 and 5 in addition to those in the 7-valent formulation.[83,84] The study in South Africa, led by Klugman and Madhi, involved 39,876 children, including approximately 2,500 of whom were HIV-infected. This study was designed to evaluate the efficacy of pneumococcal conjugate vaccine (PCV)-9 against radiographically confirmed pneumonia and vaccine-serotype IPD. The results from this study were the first in industrialising countries to demonstrate that PVC9 was able to reduce vaccine serotype-specific IPD by 83% in HIV-uninfected children and by 65% in fully vaccinated HIV-infected children.[83] Despite the lower efficacy of the vaccine in HIV-infected children, who by now were contributing to 75% of all IPD in the population under study in Soweto (Johannesburg, South Africa),[71] vaccination was nevertheless associated with an 18-fold greater reduction in the absolute burden of IPD being prevented in HIV-infected compared to HIV-uninfected children.[83] Challenges in reducing the burden of IPD in HIV-infected children, however, continued to being an issue, with longer follow-up of this cohort up to 5.3 years of age, indicating waning of immunity and protection against vaccine serotype IPD in HIV-infected, but not in HIV-uninfected children.[85] In a series of studies, Madhi *et al* also demonstrated that the lower protection against IPD in HIV-infected children was most likely a consequence of inferior immune responses to the primary series of PCV, particularly in severely immunocompromised HIV-infected children in the absence of antiretroviral treatment.[86,87] Also striking was the inferior functionality of antibody as measured by opsonophagocytic activity assays in HIV-infected children, despite similar quantitative antibody responses compared to HIV-uninfected children.[86] Madhi *et al* also subsequently demonstrated the loss of memory responses in HIV-infected children not being treated with antiretroviral therapy five years following the primary series of PCV, whereas memory responses persisted in HIV-uninfected children.[88] Nevertheless, the results from this study resulted in South Africa being the first African country and among the first of any industrialising country in which PCV was introduced into the public immunisation programme in 2009, despite it increasing the cost of the immunisation programme eight-fold.

Additional studies of PCV which preceded the vaccine efficacy trial included studies by Dr Nontombi Mbelle, then a microbiologist in the Pneumococcal Diseases Research Unit, which was among the first to demonstrate the effect of PCV vaccination in reducing the risk of nasopharyngeal colonisation by vaccine serotypes. Although no overall effect against the prevalence of colonisation by pneumococci independent of serotype was demonstrated by this early and subsequent studies,[89,90] the effect of reducing the risk of colonisation by vaccine serotypes which were the dominant causes of IPD in young children, was subsequently shown in the United States to have a profound effect in preventing IPD in vaccinated and unvaccinated members of the community.[91] This effect, known as 'indirect protection', was attributed to PCV resulting in an interruption of vaccine serotype transmission from young children who were traditionally the reservoir of colonisation in the community to other susceptible community-members. The 'indirect protection' of having PCV introduced in South Africa is currently under study by Von Gottberg. There were also a number of studies in which the immunogenicity of PCV was studied in HIV-uninfected and HIV-infected children These included the initial studies by Mbelle and Huebner *et al* in which PCV was shown to be highly immunogenic in African children,[89] as well as studies which demonstrated similar antibody responses resulting from two doses compared

to three doses of PCV and memory responses being demonstrated at 15 to18 months of age.[92,93] More recently, Madhi *et al*, in addition to the earlier studies involving HIV-infected children not receiving antiretroviral treatment, have expanded this work to examine the effect of HIV exposure in HIV-uninfected children and the effect of timing of antiretroviral treatment in HIV-infected children on the quantitative and qualitative antibody responses to PCV. These immunogenicity studies were undertaken in the Respiratory and Meningeal Pathogens Research Unit (formerly known as the Pneumococcal Diseases Research Unit which was initially awarded to Klugman) which is now under the co-directorship of Klugman and Madhi and the chief scientist in the laboratory being Dr Peter Adrian. The results from these studies indicated that the immune responses to PCV were not affected by HIV infection status in children who were initiated on antiretroviral treatment at the time of receipt of their primary series of PCV; however, delaying antiretroviral treatment was associated with functionally impaired immune responses to PCV.[94,95] Further studies on newer formulations of PCV, including a 10-valent vaccine which includes serotype 7F in addition to the serotypes included in the 9-valent formulation and which includes protein D found in *Haemophilus influenzae* as a conjugate protein, are also currently being undertaken in HIV-infected and HIV-uninfected children by Madhi *et al.*

In addition to demonstrating a reduction in IPD, the critical PCV study in South Africa also demonstrated the efficacy of the vaccine in reducing hospitalisation for pneumonia in HIV-infected and HIV-uninfected children.[83] This was critical to advocating for the widespread implementation of PCV in Africa, as non-bacteraemic pneumococcal pneumonia is the leading cause of morbidity and mortality associated with pneumococcus in children.[96] The studies by Klugman and Madhi *et al* indicated that vaccination was associated with a 25% reduction in radiographically confirmed pneumonia in HIV-uninfected children. Additionally, although the reduction in radiographically confirmed pneumonia was not significant in HIV-infected children (13%, $p>0.05$), the study nevertheless demonstrated that the absolute burden of clinical pneumonia prevented in HIV-infected children was nine-fold greater compared to HIV-uninfected children.[83,97]

Further analysis of the PCV study has also contributed to enhancing our understanding of the clinical presentation of pneumococcal pneumonia, as well as the interaction of the pneumococcus with respiratory viruses and other pathogens. In addition to establishing that the burden of non-bacteraemic pneumonia prevented by PCV9 was 7.5-fold greater than the burden of bacteraemic pneumonia prevented, the vaccine study also uncovered that bacteraemia was approximately four-fold more common in HIV-infected compared to HIV-uninfected children with pneumococcal pneumonia.[97] Further insights into the pathogenesis of pneumococcal pneumonia related to the observation that children who received PCV9 had a one-third reduction in the incidence of hospitalisation for pneumonia in which respiratory viruses were identified.[98,99] These findings suggested that at least one-third of all hospitalisations in children among whom viruses were identified previously were attributable to a super-imposed pneumococcal infection instead of being a direct complication of the respiratory viral infection. Specifically, hospitalisation for pneumonia associated with influenza virus was reduced by 44% and there was also a similar reduction in hospitalisation rates for pneumonia associated with the recently discovered human metapneumovirus.[98,99]

International working groups

South African researchers have also made considerable contributions to international working groups focused on pneumococcal disease. Klugman and Leslie McGee set up a global network of researchers to track the global expansion of pneumococcal clones under the auspices of the International Union of Microbiological Societies (IUMS) and this network continues to contribute to our knowledge of the global spread of pneumococcal clones.[100] Klugman was also part of a WHO working group to establish pneumococcal carriage guidelines,[101] and a further WHO group to establish serological criteria for licensure of conjugate vaccines.[102] Additionally, Klugman and Madhi contributed to the development of WHO guidelines for standardising the interpretation of chest radiograph interpretation to enable comparability between pneumococcal conjugate vaccine trials,[103] as well as inputting on the serological criteria for licensure of new PCVs.[104]

Outreach to other countries in sub-Saharan Africa

The detection of antimicrobial resistance in the pneumococcus and its implications, particularly for the treatment of meningitis, require surveillance systems and microbiology laboratory capacity that are severely lacking in most other African countries. One way to do this is to establish pneumococcal resistance patterns in carriage strains which are predictive of the levels of resistance in the community. The Respiratory and Meningeal Pathogens Research Unit has been involved in a number of such activities including studies organised by Huebner and Avril Wasas in Zambia,[105] Botswana,[106] Lesotho,[107] Malawi[108] and the Central African Republic.[109]

Conclusion

South African scientists and clinicians have consistently been in the forefront of attempts at preventing and improving the management of pneumococcal disease, particularly among the most vulnerable sections of our population and history will judge their worth. In the meantime, South Africa and the world owe a special tribute to Robert Austrian, not only in recognition of his contributions to vaccine evaluation and use but also for his insights and appreciation of pioneer research

performed in South Africa and his ability to learn from these endeavours and improve on them. Not quantifiable are the thousands of lives of miners saved by the contrasting efforts of Sir Spencer Lister by vaccination and AJ Orenstein for improving healthcare and living conditions of miners, and in the process not only saving lives but also enhancing the quality of life. Whilst battles against the pneumococcus and pneumonia have been won and tremendous inroads have been made in combating this leading global cause of morbidity and mortality, much remains to be done before the war against the 'captain of the men of death' can be declared as being won.

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