REPORT

Clinical Management and Prevention of Septicaemia and Meningitis in Children and Adults: An Update

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Meningitis is an inflammation of the lining that covers the brain and spinal cord (the meninges) which can develop very rapidly. It is usually caused by a bacterial or viral infection. Bacterial meningitis is generally more serious than viral meningitis and there are many types of bacterial meningitis including those caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib) and group B *Streptococcus*. Most people recover from the disease, but it can leave permanent disability. On the other hand, septicaemia is a type of blood poisoning, which can be caused by the same bacteria that cause meningitis. It often accompanies meningitis and can progress to coma and death. Septicaemia can reduce the amount of blood reaching vital organs, such as the liver and kidneys. Meningitis and septicaemia are the commonest cause of death among children aged one to five years, and the most common infectious disease causing death in children and young people in several regions of the world.

The international conference "Meningitis and Septicaemia in Children and Adults´ 2007" was organized by the Meningitis Research Foundation (MRF), which funds research to prevent meningitis and septicaemia and to improve survival rates and outcomes. The Foundation also promotes education and awareness to reduce death and disability, and gives support to people affected. The Conference was held at the Royal Society of Medicine, London, United Kingdom (UK), on 7-8 November 2007. This was the sixth scientific conference that the Foundation has held. Conferences normally take place every 2 years.

Day 1 of the conference was devoted to the Clinical management of meningitis and septicaemia in children and adults. During the day the speakers were divided into four sessions. The first session was named Recognition of the child with sepsis or meningitis in primary and secondary care -a story with a NICE ending? First, Dr. Nelly Ninis, from the St. Mary´s Hospital, London, presented the results of a study of Healthcare Delivery and the Outcome of Meningococcal Disease in Childhood, funded by MRF. Such study provided the investigation team with hospital data on 500 children with meningococcal disease. They showed that failures in hospital management led to inadequate care of those children and a worse outcome. An important factor in good early management of cases with meningococcal disease was prompt recognition of both the disease and the complications of disease. The study highlighted the important role that primary care physicians should play by adopting a standard approach to paediatric assessment similar to the one conducted in secondary care. Dr. Matthew Thompson, from University of Oxford, discussed the results of two recent studies which attempted to determine the diagnostic value of presenting symptoms and vital signs for identifying children with serious bacterial infection in primary care and paediatric assessment units. The discussion of the results of those studies suggested modifications to the clinical assessment of children in primary care. Similarly, Dr. Roderick MacFaul, from Pinderfields Hospital, Wakefield, presented preliminary results of two studies comparing initial measurements of vital signs in children with viral and bacterial infection. Early analysis suggests that reliance on overall clinical impression or individual vital signs alone offers less precision than when overall clinical assessment is taken together with clustered vital signs using an arbitrary scoring system. Preliminary results suggest that the statistical performance of the assessment is somewhat improved by the mentioned approach. To end the first session, Dr. Martin Richardson, from Peterborough District Hospital presented the National Institute for Health and Clinical Excellence (NICE) guideline "Feverish Illness in Children: assessment and initial management in children younger than 5 years" published in May 2007. The guideline was commissioned by the Department of Health of UK and used the most thorough evidence-based medicine techniques to produce recommendations that encourage healthcare professionals in primary and secondary care to take a standardised approach to the management of children presenting with feverish illness.

The second session, named Epidemiology and Treatment, started with a presentation given by Dr. Edward Kaczmarski, from Meningococcal Reference Unit, Health Protection Agency, Manchester, about the current trends in meningitis and septicaemia in the UK and Europe. The three most common organisms causing bacterial meningitis in those territories are *N. meningitidis*, *H. influenzae* and *S. pneumoniae*. European surveillance of invasive meningococcal and *Haemophilus* infections has been in place since 1999 and the variation in the absolute and relative incidence of invasive meningococcal and *Haemophilus* infections is marked. Vaccination against Hib and meningococcal serogroup C infections has substantially altered the pattern of infection. The European Centre for Disease Control plans to introduce surveillance for pneumococcal infection during 2008. According to the presentation of Dr. Kaczmarski, continued laboratory surveillance is essential to monitor threats such as the emergence of strains that escape vaccination and to

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outline the potential role of new vaccines, including tetravalent conjugate vaccines.

Professor Robert Heyderman, from the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, presented an update on antibiotic choices for the clinical treatment of meningitis. Since the development of sulphonamides, chloramphenicol and penicillins, there has been a dramatic improvement in outcome of patients with acute bacterial meningitis. Except in few cases, antibiotics should be administered empirically to all patients with suspected bacterial meningitis. The final choice of antibiotic will depend on several variables including the age of the patient, underlying co-morbidity, the likely pathogens and the local antibiotic susceptibility patterns. At present, third generation cephalosporins form the cornerstone of therapy. The value of new agents for the treatment of penicillin resistant pneumococci, the duration of antibiotic therapy and the impact of adjunctive steroids on antibiotic efficacy were some issues discussed by Professor Heyderman.

An overview about the future therapies and clinical management of adult sepsis was presented by Professor Jon Cohen, from Brighton & Sussex Medical School. According to his talk, Activated Protein C remains the only licensed 'new' or novel therapy for adult sepsis, but debate and discussion about its place in therapy continue. New trials are being developed that will look at dose-regulated therapy based on Protein C levels, and also at restricting its use to the most severe subgroups of patients. In the last years, other investigations in this field included the evaluation of 'goal directed therapy', tightly-controlled insulin therapy and low dose steroids. However, questions continue to be asked about the widespread applicability of these approaches. Further new strategies, like those directed at the Toll-like Receptor pathway, are under development. Clinical investigators continue working to refine 'standard' approaches to therapy, including the optimal management of antibiotics.

Two oral presentations were included in the session named Current and future treatment of sepsis and meningitis. Dr. Simon Nadel (St Mary's Hospital, London) spoke about the potential therapies for childhood meningococcal disease and sepsis. It is widely known that sepsis is a common clinical problem, responsible for an increasing number of deaths. Many new therapies for severe sepsis have been developed, but few have shown benefit in rigorous clinical trials. The only adjunctive therapy supported by strong evidence of benefit is Activated Protein C. However, no experimental therapy has proven beneficial in children with sepsis. Promising new strategies are the neutralisation of the triggers of inflammation such as endotoxin and inhibition of the signal transduction mechanisms. Statins may be beneficial in prevention of sepsis and as adjunctive treatments. Reconstitution of the immune response with interferon-gamma or granulocyte-macrophage colony stimulating factor may reverse immunoparesis in severe sepsis. Many other molecular targets have been identified for possible therapeutic intervention, but there are still fundamental difficulties to be overcome in demonstrating efficacy in clinical trials. The talk discussed how advances in management of sepsis can be extrapolated to use in children. Later in the session, Dr. Guy Thwaites, from the Imperial College, London, reviewed the major questions concerning the clinical management of tuberculous meningitis. The diagnosis and management of tuberculous meningitis is difficult. The clinical features are non-specific, conventional bacteriology is widely regarded as insensitive, and newer diagnostic methods are incompletely evaluated. Treatment involves four drugs and they only prevent death or disability in less than half of sufferers. Outcomes are significantly worse in those infected with HIV and with disease caused by *Mycobacterium tuberculosis* resistant to the major first-line agents. According to Dr. Thwaites, tuberculous meningitis caused by bacteria resistant to isoniazid and rifampicin is becoming more common and is almost always fatal within eight weeks of presentation unless second-line drugs are given. He summarized the priorities for future research, which include the development of a simple, highly sensitive, rapid diagnostic test; novel methods to detect disease caused by drug resistant organisms; and determining the role of fluoroquinolones and other second-line agents in treatment.

The last session of Day 1 was named Advances from research - prospects for diagnosis and treatment of meningitis and septicaemia. Two speakers presented their contributions in that session. In his lecture, Dr. Robert Tasker (Cambridge University School of Clinical Medicine, Addenbrooke's Hospital) spoke about present and future neuroprotective strategies to reduce brain injury in meningitis. He explained the fundamentals of perturbation in oxygen, carbon dioxide and perfusion pressure and their effects on the child's brain during critical illness. The lecture focused on two broad topics: Ischaemia and acute neurotoxicity and Critical cerebral perfusion. In the first topic, Dr. Tasker discussed about areas of acute neurotoxicity gaining interest, like the cerebral inflammatory response, ischaemic preconditioning and ischaemic tolerance, the pH paradox and brain repair. The last speaker of the session was Professor Michael Levin, from Imperial College, London, who presented an update on how the application of gene expression profiling, proteomics and high throughput genotyping is providing new insights into the pathophysiological mechanisms as well as new tools for diagnosis of different forms of meningitis and septicaemia. The development of high throughput gene expression profiling together with proteomic methods to analyse the full range of expressed proteins has provided powerful new tools for understanding the inflammatory process triggered by infection. These new tools offer both new understandings of the infectious disease mechanisms and new methods for diagnosis.

The second day of the conference was devoted to the Prevention: Public Health, vaccine programmes and development. The programme started with a Satellite Meeting, sponsored by Wyeth Vaccines, named Evidence-based prevention of pneumococcal disease. The speaker was Dr. Robert George, from UK, who explained how the UK surveillance system facilitates improvement and adaptation of standard vaccination schedule to prevent pneumococcal disease.

For the main programme of the day, the speakers were divided into four sessions. The first session,

named Current Vaccines, started with a conference presented by Dr. Jane O´Hallahan, from the New Zealand Ministry of Health. New Zealand (NZ) has experienced a *N. meningitidis* serogroup B epidemic since 1991. MeNZB™ is a strain-specific outer membrane vesicle (OMV) vaccine made using a NZ epidemic strain isolate, NZ98/254 (B:4:P1.7b,4), from two manufacturing sites, the Norwegian Institute of Public Health and Chiron Vaccines (now Novartis). This vaccine showed to be safe, immunogenic, and non reactogenic in the observer-blind trial with 8-to 12-year-old children. The effectiveness of this vaccine was assessed in a prospective observational study following a nationwide vaccination program in NZ. The vaccination program began in July 2004, and the study used data from January 2001 to June 2006. The mass campaign concluded on June 30, 2006, and now MeNZB™ is included in the National Childhood Immunization Schedule. Dr. O´Hallahan indicated that over a 2 years-period, 80% of all those under 20 years old completed the vaccine course and high coverage was achieved in those at highest risk of disease. In her lecture, she commented that the mass immunization program to control an epidemic has been a proven success with reduction in the number of reported cases of the disease which confirms the effectiveness of the vaccine.

In the second talk of the session, Professor David Goldblatt, from University College London, gave an update on the UK experience with a reduced pneumococcal conjugate vaccine priming schedule. In preparatory studies, designed to inform the introduction of a heptavalent vaccine in the UK (Prevenar®, Wyeth Vaccines), a reduced priming schedule of two doses of a similar nine-valent pneumococcal conjugate vaccine (delivered at 2 and 4 months of age) was compared to a three dose priming schedule, with a booster for both groups administered at 12 months of age. The results of this comparison provided the evidence base for the introduction of a 2+1 pneumococcal conjugate vaccine schedule in the UK, with Prevenar® being administered at 2, 4 and 12 months of age together with the other childhood immunizations.

The last speaker in the Current vaccine's session was Dr. Andrew Pollard, Head of the Pediatric Infection and Immunity Laboratory at the University of Oxford, who presented an update about prevention of meningococcal disease in the UK. Serogroup C meningococcal conjugate (MCC) vaccines, first launched in the UK in 1999, have been used successfully in Australia, Canada and several other European countries. Combination conjugate vaccines, containing more than one meningococcal polysaccharide, have been developed to broaden protection against the disease. The development and introduction of this vaccine has resulted in a dramatic reduction in the incidence of serogroup C infections in UK, from 983 reported cases in 1999 to 58 in 2004. Actually, *N. meningitidis* serogroup B (MenB) disease remains a significant public health problem in UK. In 2006 there were 1.057 laboratory confirmed cases of MenB disease, which represents approximately 90% of all laboratory confirmed cases in England, Wales and Northern Ireland. Dr. Pollard explained that most cases are now caused by this serogroup, but there were 50-183 laboratory-reported cases caused by other serogroups each year over the past decade, mainly serogroup W135 or Y. Tetravalent conjugate vaccines in the UK could have a role in broadening protection by strategic placement in the schedule, perhaps as a booster vaccine. The potential use and impact of these vaccines on disease in the UK will be considered. Several new group B vaccines have shown the potential for protection against a proportion of serogroup B strains in preclinical studies and are now in clinical trials. Although estimates of protection are difficult to establish for MenB vaccines, a partially protective vaccine could reduce meningococcal disease in the UK by at least as much as was seen after introduction of the MenC vaccine.

The second session was entitled Prospects for defeating meningitis in developing countries. Dr. William Perea from the World Health Organization (WHO) revised the progress on meningococcal vaccines for Africa. In the countries of the African "meningitis belt" in sub-Saharan Africa, meningococcal meningitis outbreaks occur every year during the dry season and large epidemics emerge approximately every 5-10 years. In that part of the world, most of meningococcal disease cases are caused by *N. meningitidis* serogroup A, but strains belonging to serogroup C and more recently serogroup W135 also have been reported. *N. meningitidis* of the serogroup A has been the cause of more than 90% of epidemics since 2003. Of particular concern is the fact that a new serogroup A strain (ST-2859) has been increasingly isolated in west Africa since 2005. This strain was responsible for the large epidemics that affected Burkina Faso in 2006 and 2007. Its increased isolation in North-East Niger during the 2007 season suggests this virulent strain is spreading to other Belt countries and may cause a new epidemic wave in the region. WHO estimates that up to 80 million individuals within the outbreak area could require vaccination over the course of the next two to three epidemic seasons. Unfortunately, the production of WHO pre-qualified meningitis polysaccharide (PS) vaccine dropped sharply between 2003 and 2005 and the expected production for 2007-2008 will be 26 million doses. A concerted effort from the international health community, the vaccine manufacturers and donor development agencies led by WHO, will be crucial to effectively face this public health challenge. Currently, a South-to-South solution to increase PS vaccine supply is ongoing. A manufacturer agreement between the Finlay Institute, Cuba, and Biomanguinhos, Brazil, to produce a Bivalent AC vaccine, was established in 2006. After prequalification, the expected production for years 2007-2008 is 15 million doses.

Dr. Kate O'Brien, from the Johns Hopkins Bloomberg School of Public Health, Baltimore, USA, and Deputy Director at the Pneumococcal Accelerated Development and Introduction Plan (PneumoADIP) from the Global Alliance for Vaccine Initiative (GAVI) presented the global burden of Hib and pneumococcal disease in children. GAVI´s PneumoADIP is an effort to assure access to pneumococcal conjugate vaccines for the world's poorest children at the earliest possible time. Current diagnostic tools for bacterial pneumonia are insensitive, and most developing countries lack such registration system. Thus, the best available option for generating country-specific estimates is to

model the burden of disease based on the best data currently available. Over 13 000 citations were reviewed resulting in over 4 000 citations included in the analysis dataset for meningitis and non-pneumonia/ non-meningitis. The WHO disease burden project helps overcome the lack of information and inadequate financing that have been major obstacles to new vaccine introduction.

Next, Dr. Simonetta Viviani, Head of Vaccine Development at the Meningitis Vaccine Project (MVP), presented an update of progress on a conjugate MenA vaccine for Africa. The MVP, a partnership between the WHO and PATH, was created in 2001 through a grant from the Bill & Melinda Gates Foundation. The project's goal is to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure and widespread use of MCC vaccines.

The vaccine, *N. meningitidis* group A PS conjugated to tetanus toxoid (PsA-TT conjugate vaccine) as the protein carrier, has been developed at the Serum Institute of India Ltd, Pune, India, using a new licensed conjugation technique from the Center for Biologics Evaluation and Research, Food and Drug Administration (Maryland, USA). A phase I clinical study has been performed in India where the MenA conjugate vaccine was shown to be as safe and immunogenic as a control licensed PS vaccine. The vaccine is under clinical testing in phase II/III clinical trials in the African Meningitis Belt countries and in India.

The third session was devoted to the future prevention of pneumococcal disease. Five presentations covered the progress in the development of new pneumococcal vaccines. The advances on a new pneumococcal/*H. influenzae* vaccine were presented by Dr. William Hausdorff, from GlaxoSmithKline Biologicals. The candidate conjugate vaccine 'Pneumococcal *H. influenzae* protein D Conjugate Vaccine' (PHiD-CV) comprises 10 pneumococcal serotypes causing invasive pneumococcal disease worldwide. It incorporates as a carrier the outer membrane protein D from *H. influenzae*, shown in pre-clinical models to protect against non-typable *H. influenzae* (NTHi) acute otitis media (AOM). This novel carrier was chosen to protect against both *S. pneumoniae* and NTHi and to simultaneously minimise the risk of immunological interference with concomitantly administered vaccines. The vaccine elicits high antibody levels against each pneumococcal serotype, and protein D conjugates are efficacious against both *S. pneumoniae* and *H. influenzae* AOM.

Dr. Susan Tansey, from Wyeth Vaccines Research presented the progress in the development of a new 13-valent pneumococcal conjugate vaccine (PCV13). Phase 1 studies in healthy adults demonstrated the safety and immunogenicity of PCV13. Phase 2 studies conducted in USA infants showed encouraging results in terms of safety, reactogenicity and immunogenicity of PCV13. Currently, phase 3 infant and toddler studies of PCV13 are in progress globally, including studies in Europe, Asia and the USA. PCV13 is also in phase 3 studies for use in adults. According to Dr. Tasey, PCV13 represents the next generation of pneumococcal conjugate vaccines with expanded serotype coverage to reduce further the burden of pneumococcal disease in infants, children and adults worldwide.

Data presented later in this session suggested that, in children, the age-related reduction in pneumococcal invasive disease precedes the development of naturally acquired antibodies to the capsule, pointing to the possibility that other mechanisms might be important. Some workers have hypothesized that antibodies to noncapsular antigens may play a significant role. The mechanisms whereby humans are protected against nasopharyngeal pneumococcal invasive disease and/or colonisation have not been elucidated. Dr. Richard Malley, from Children's Hospital Boston, USA, is leading an international effort for the manufacture of a pneumococcal whole cell-killed vaccine (WCV) for use in developing countries. Several years ago, they began evaluating the possibility of developing a killed, whole cell pneumococcal vaccine for intranasal administration. Using different animal models, they showed that this WCV protects against invasive pneumococcal disease (including meningitis) and colonization by a variety of serotypes. With the support of PATH, and in collaboration with Instituto Butantan in Brazil and University of Goteburg in Sweden, they are now preparing a Good Manufacturing Practices-grade whole cell vaccine for clinical studies.

Professor Adam Finn, from University of Bristol, also contributed to the same topic, by presenting results on the T-cell immunity to the candidate whole cell killed pneumococcal vaccine. In particular, the whole cell vaccine protects against nasopharyngeal colonization by an antibody-independent CD4+ T cell-dependent mechanism. The conclusion of the study conducted by Professor Finn and co-workers is that WCV induce both total and naïve T-cell proliferation in a dose-dependent fashion in human adenotonsillar cells. Pneumolysin may mediate these effects. This study underlined the potential importance of pneumolysin in inducing respiratory tract mucosal T-cell immunity against pneumococcal infection and reinforces evidences supporting its potential use as a vaccine antigen.

Dr. Jan T. Poolman, Vice-President of Research and Development within Bacterial Vaccines at GlaxoSmithKline, in his presentation highlighted the importance of common pneumococcal proteins as candidate vaccine antigens. The selection of a short list of pneumococcal proteins was described after an intensive antigen discovery effort that included genomic mining, recombinant expression and preclinical animal model evaluation. Pneumococcal proteins can be a valuable addition to conjugates to further extend coverage and possibly prevent serotype replacement.

The last session of the meeting was Outlook for prevention of Group B meningococcal disease, and three presentations contributed to it. Dr. Ray Borrow from the Health Protection Agency, Manchester, UK, presented an overview of progress on MenB vaccines and correlates of protection. According to the experience accumulated after the administration of OMV and group C MCC vaccines, the next generation of MenB vaccines will be licensed on the basis of immunogenicity and safety data, rather than efficacy studies. A prospective MenB vaccine will be expec-ted to elicit satisfactory serum bactericidal antibody (SBA) titres

against a range of diverse MenB strains. This surrogate was derived from data from efficacy and immunogenicity studies of OMV vaccines conduc-ted in various countries. Also, an inverse relationship between putatively protective SBA titres and the incidence of disease by age was described by Goldschnei-der, *et al.* in the 1960s in the United States. However, recent data from the UK do not mirror this relationship. In order to develop the universal meningococcal vaccine a variety of approaches are now well progressed. These include reverse vaccinology, recombinant antigens and up-regulation of minor conserved antigens.

Neisseria lactamica is a commensal of the upper respiratory tract which is often carried by infants and young children; epidemiological evidence indicates that colonization with this bacterium can elicit SBA against *N. meningitidis.* Researchers at the Health Protection Agency of UK have developed a meningococcal disease vaccine based on *N. lactamica* OMV, using methods developed for meningococcal OMV vaccines. Related to this approach, Dr. Andrew Gorringe, leader of the Meningococcal Vaccine Research Group in that Agency described the preliminary results of a phase I safety and immunogenicity trial in adult male volunteers. Serology results from a subset of vaccinees showed that the vaccine is immunogenic, demonstrated by an approximate four-fold rise in *N. lactamica*-specific IgG geometric mean titre following three doses of *N. lactamica* vaccine. IgG cross reactive to OMVs from six meningococcal strains has also been observed following three doses of *N. lactamica* vaccine. This seems to be a considerably different approach to achieve protection against MenB.

In the last conference of this intense meeting, Philipp Oster, MD, Head of Development of Meningococcal B Vaccines in Novartis Vaccines and Diagnostics, presented some recent advances in vaccine development for meningococcal serogroup B disease achieved by Novartis Vaccines. They applied a breakthrough technique known as 'reverse vaccinology' to develop a safe and broad-coverage vaccine, by identifying those antigens which are surface-exposed in meningococcus and induced a SBA response against a broad panel of disease-causing strains. The final immu-nogen combines three recombinant protein antigens (two fusion proteins and one single polypeptide) with the OMV component of the MeNZB™ vaccine. The Phase I study in adults, which constituted the Proof of Concept of this candidate vaccine, indicated that the preparation elicited SBA against three strains, which belong to different clonal complexes and serosubtypes. These encouraging results conducted to a Phase II study in UK infants. According to the preliminary results presented in the meeting, the Novartis MenB vaccine is the first vaccine based on recombinant proteins to demonstrate bactericidal immune response in adults and infants.

In parallel to the oral presentations, more than 40 posters were displayed all over the meeting. The posters covered important aspects of the treatment and prevention of meningitis and septicaemia in children and adults. The work presented by Bridget Gollan, from the Department of Microbiology, Centre of Molecular Microbiology and Infection, Imperial College, London, received the Award for Best Poster Presentation. Her poster was entitled Identification and characterisation of meningococcal strains that are resistant to serum bactericidal activity elicited by the group C MCC vaccine.

At the end of the meeting there was a Round-up discussion on how near is implementation of the issues recommended during this informative and productive event. An invitation for the international conference to be held in 2009 closed the intense days of scientific exchange and networking provided by this important meeting.