An overview of pneumococcal infection and vaccine development discussed at the 5th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD)

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Introduction

Streptococcus pneumoniae is a Gram-positive bacterium and a major human pathogen, also known as pneomococci. It has about 90 known capsular polysaccharide types (serotypes) with a large variety of surface structures [1]. It colonizes the upper respiratory tract, and under normal conditions it lives and grows in the nasopharynx, where it establishes commensalism. However, the disturbance in the host-pathogen homeostasis, for example through viral infections, malnutrition or local damage of the mucosa, is associated with bacterial invasion and disease development [2, 3]. The pneumococcus is a major cause of an array of diseases such as acute bacterial sinusitis, meningitis, and bacteremia. It remains the major causative agent of acute bacterial pneumonia and otitis media.

Pneumococci clearance from the lung mainly results from phagocytosis and the intracellular killing of the bacteria by neutrophils and alveolar macrophages. This process can only occur in the presence of type-specific immunoglobulins (IgG1 and IgG2, IgM and IgA) and an activated complement. Pneumococci may escape this mechanism in the absence of serotype-specific antibodies, and consequently, it may enter the host through the interstitial tissue of the lung, resulting in lymphatic spread and subsequent blood stream invasion causing bacteremia [4]. The mechanism of clearance from the blood appears to depend on the interaction of type-specific antibodies (IgG), complement and phagocytic cells in the liver and spleen [4].

Worldwide, approximately 1.1 million deaths each year are attributed to *S. pneumoniae* infection. Therefore, the prevention of pneumococcal diseases has become of great interest. Despite the availability of excellent antimicrobial therapy and adequate health care systems, respiratory diseases and invasive infections caused by pneumococci are still a major health problem. Recently, antibiotic resistance has become a worldwide concern, limiting the choice of antimicrobial agents. Until now, many research groups have focused on the development of new effective vaccines to be used in particular risk groups. Although the 23-valent polysaccharide vaccine is immunogenic and protective in most adults [5] and children over 5 years of age, it fails to protect children of less than 2 years of age. Fortunately, the recent conjugated vaccines have shown high efficacy in preventing invasive diseases in this risk group [6, 7]. Moreover, promising results regarding the prevention of pneumonia and acute otitis media have been published [8, 9]. Unfortunately, protection is raised against a reduced number of pneumococcal serotypes, with a limited worldwide coverage of this vaccine. Therefore, serotype replacement and subsequent vaccine failure have become a serious concern. Moreover, several pneumococcal surfaces are currently considered as alternative vaccine candidates because of their serotype-independence.

Hence, the scientific approach on this topic is updated and followed up every two years at The International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD), with more than 500 delegates from 64 countries participating in the recent 2006 5th edition of ISPPD held in April 2-6 in Alice Spring, Australia. One hundred and fifteen oral presentations and 299 posters were organized within 14 symposia discussing important topics including: Genetic and Molecular Aspects of the Pneumococcus, Diagnostic and Technology, Global Epidemiology of Pneumococcal Diseases and Resistance and Serotype, Pneumococcal Diseases Pathogenesis-Biofilm and Viral Infection, Immune Status and Susceptibility, Evaluation of Current Conjugate and Polysaccharide Pneumococcal Vaccines and Animal models for protein pneumococcal vaccines. An overview of current achievements and future trends are presented in the following sections, with a special emphasis on animal models for vaccine standardization.

Molecular issues and pathogenesis

A noteworthy advance was achieved in pneumococcus genetic and molecular issues, unraveling mechanisms of pathogenesis and drug action. New genes responsible for the synthesis of the capsular polysaccharide and antibiotic resistance were identified, opening strategies in targeting and interfering pneumococcus persistence through more effective therapies and vaccines. The application of novel genotyping methods such as multilocus sequence typing (MLST) were proposed for harmonizing the results of different laboratories, and aiding in the global epidemiology follow up. This could also facilitate genotype epidemiological distribution surveillance in different immunized populations.

Pathogenesis of pneumococcus diseases is a complex multi-step process, which starts with the colonization of the nasopharynx by *S. pneumoniae*. Humans are the only known host for this organism, and its capacity to occupy the nasopharyngeal niche is essential, not only for producing of diseases, but for transmitting the organism in the population. From an evolutionary perspective, the pneumococcus would benefit more by establishing a long-term commensalism with its human host, than by causing invasive diseases. The progression from carrying to having the disease is a relatively uncommon event, but the consequences for the host are

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significant and the global burden of pneumococcal diseases remains enormous. Several presentations brought insights into pneumococcal disease pathogenesis. The complex multi-step process appears to be highly dependent on virulence factors such as pneumolysin and capsule proteins which can increase the duration and density of the carrier state and, therefore, the risk of the invasive disease. Besides, it was recently reported that some pneumococci produce previously unknown adhesive pili-like appendages on their surface extending beyond the polysaccharide capsule, which enhances nasopharyngeal colonization and contributes to virulence in a systemic challenge model. Additionally, piliated pneumoccoci elicited a higher TNF-α response during systemic infection, compared with non-piliated derivatives, suggesting that pneumococcal pili not only contribute to adherence and virulence but also stimulate host inflammatory response. Other proteins have been shown to be involved in adherence, colonization and surviving of pneumococci, like FBA and ABC transporters. Pneumococcal cell wall components such as teichoic acid have also been studied in relation to endothelial cell receptors and cardiac function and sepsis-associated neural damage. The results presented at this Symposium contribute to our understanding of the complex interaction between pneumococci and humans, and enable the identification of a novel virulence factor while also unraveling new targets for vaccine candidates and therapies now under development.

Otitis media

Otitis media (OM) may not have the same level of life-threatening sequelae as pneumonia and invasive diseases caused by *S. pneumoniae*, but it is a significant condition for young children. The lack of otological immunology knowledge hinders the understanding of otopathogens, otopathogenesis and improving mechanisms for treating and preventing OM. A recent study revealed that certain response genes, in particular those associated with TNFα and IL-6 production, showed polymorphism that may affect the production of these cytokines in OM. Polymorphism within the CD14 promoter in the T allele CD14C-159T resulting in increased levels of soluble CD14 may also be a differential factor between otitis prone and non otitis prone children since CD14 plays a key role in innate immunity. Another important aspect is the association of the AOM with biofilm, a hypothesis first observed in chinchilla and recently corroborated in humans by Hall-Stoodley L. They detected bacterial biofilms on the middle-ear mucose of children with chronic otitis media [10]. This may help explain the lack of antibiotic efficacy for this disorder, given that biofilm bacteria show more antibiotic resistant than single cells in suspension [11-13]. Furthermore, the biofilm provides a physical barrier that enhances pathogen resistance to host defenses such as opsonization, lysis by the complement and phagocytosis [14] which involve new analyses on how to prevent or eliminate AOM.

Diagnostic and detection

The detection of pneumococci by bacterial culture, PCR or antigen detection is of critical importance to pinpoint the exact role of the pneumococcus as the leading cause of global morbidity and mortality of infectious origin. Blood culture is still one of the critical tests and quality assurance/control allowing standard practices is neededed. Blood volume and preventing contamination are relevant parameters; the implementation of a pediatric micro-culture system is to be considered. The non-culture detection of pneumococci is a developing field. Common-polysaccharide (CPS) antigen detection in the blood and cerebrospinal fluid (CSF) and PCR detection of pneumococci in nasopharyngeal swabs, the blood and CSF are potentially good for improving pneumococcal detection rates. Antigen and DNA-PCR detection methods for determining serotype are also being developed. The tragert in this field is to achive tools producing a fast detection and serotyping of the circulating strain, since this is the a key to epidemiological control worldwide.

Epidemiology

On analysing the global epidemiology of pneumococcal disease, a significant increase of pneumonia and meningitis due to *S. pneumoniae* was found worldwide. But a huge differences was observed between industrialized and developing countries; for example the incidence of invasive pneumococcal diseases (IPD) in children under 5 years of age Mozambique two years ago was 416/100.000, in Kenya it was 137/100.000 and in Papua New Guinea of 1150/100.000 compared with 12.4/100.000 in USA and 56/100.000 in the White Mountain Apache American Indian Community although the impact itself of vaccination has not been observed in indigenous communities. Most deaths occur in the developing world due to the high rate of IPD. Moreover, pneumococcal disease occurs mainly in at young ages but it is a significant burden in some high-risk groups with depressed immunity such as with HIV infection and certain ethnic or Indigenous populations where children are live under crowded conditions.

Immunity and Vaccine Developments

In regard immunity and susceptibility, there was a switch in the point of view of the immune response to pneumococcus, from considering that antibodies have a key role in the protection and prevention of colonization at themucosal level and the invasive disease, to giving more importance to cellular mechanisms. There was an increase in the number of studies related to antibody independent host defense mechanisms in pneumococci including T cells, cytokines, chemokines and cells from the innate immune system. Therefore, the new candidate vaccine under investigation can be extensively evaluated before it is considered to be protective or not against pneumococcal diseases. Despite the increase in the evidence on the interaction of the pneumococcus with the immune system, the roles of the different weapons of the immune response in protection must still be fully elucidated.

Five years after licensing the Prevnar® vaccine, studies on its the application in the USA and its later surveillance showed a significant decrease in the disease burden in children and in the elderly [15] . Similar results were obtained in Australia, Finland and the UK. Moreover, the long term follow-up of children from Finnish OM trials suggests that the vaccine had a substantial impact on the incidence of chronic OM. Nevertheless, in Germany where the vaccine has 70%

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coverage, there was an increase from 78% to 85.5% in the number of meningitis cases. The coverage of the currently conjugated vaccine will be as low as 43% in South Asia, 63% in Latin America and very variable in Africa due to recent outbreaks of serotype 1 regional differences in capsular types that cause infection in children. The failure to cover all polysaccharide types is greater problem in adults than in children, because the clinically important infections in adults are caused by a larger variety of strains with different capsular types than that one causing the disease in children. These aspects must be considered when increasing vaccine coverage in the world. Furthermore, a second vaccine containing 10 serotypes is expected to be licensed in 2008, and more than 20 vaccine candidates are in the pipeline with the objective to extend worldwide coverage. An additional concern is that the new polysaccharide-protein conjugate vaccines will probably be too expensive for worldwide vaccination, mainly in the developing world.

The cost of the conjugated vaccine has been the main reason why the application of this vaccine was reduced to a few developed countries in which it was only applied to high risk groups. In order to reduce the number of doses and the age of vaccination, a novel schedule of vaccination was tested in the UK. Similar immune responses were obtained by all serotypes except for serotype 4 on comparing the administration of two doses of the conjugated vaccine, the first given at birth, with the schedule at doses applied at 2, 4 and 6 months. Despite the differences in serotype 4, 100% of the newborn group achieved on antibody concentration greater than the putative protective threshold of 0.35mcg/ml [16]. Lately an increase of the use of the unconjugated polysaccharide vaccine in several countries has been reported [17]. However, there is evidence on the risk of the so called hyporesponsiveness due to the excessive application of free polysaccharide vaccines, but this phenomenon must be fully studied.

Furthermore the evidence from the Prevnar® vaccination studies also demonstrated a beneficial effect on disease morbidity, a shift in the begining of the emergence of the disease due to non-vaccine serotypes is well demonstrated. This phenomenon also called serotype replacement was observed in others where the vaccine was applied massively such as USA and Australia and countries where it was only applied in private clinics as in Spain. The serotype most frequently observed as the replacement is serotype 19A even when the related serotype 19F was included in the Prevnar vaccine. Isolated strains before and after the conjugated vaccine administration showed similar genotypes suggesting a capsule switch through serotype selection. These results bad to the need of vaccine development based on non capsular antigens.

Several new strategies to generate non polysaccharide pneumococcal vaccines are under study. The new strategies intend to solve the problems of polysaccharide immunization and include killed whole-cell, peptides mimicking polysaccharide vaccine to protect against nasal colonization (intranasal alternatives) and protein-based vaccines.

In the last decade, several groups have studied the use of pneumococcal proteins as potential vaccine candidates with promising results. Although many proteins including pneumolysin, pneumococcal surface protein A (PspA), pneumococcal surface adhesion A (PsaA), cholin binding protein A (CbPA), neuraminidase, and autolysin have been suggested as potential candidates, the proteins PspA, PsaA and pneumolysin are currently the leading vaccine candidates [18]. Thus far pneumococcal surface adhesion A (PsaA) and pneumolysin have proven to be highly protective against colonization and invasive disease in animal models respectively [19]. Moreover, active immunization with PspA in animal models has proven protective against invasive and nasopharyngeal carriage [19-21]. Moreover, the immunization of human proteins with recombinant proteins elicited broadly cross-reactive antibodies to heterologous PspA molecules [22]. Furthermore, these antibodies were found to protect mice challenged intraperitoneally with pneumococci [23, 24]. After sequencing the genome of two *S. pneumoniae* strains the work to identify of new candidate protein vaccines by genomic studies has increased by applying, numerous bioinformatics tools. Such is the case of the fructose bis-phosphate aldolase surface protein (Flamingo cadherin) which is involved in pneumococci adherence to lung epithelial cells [17]. Antibodies elicited by these proteins inhibited the binding of pneumococcus to lung epithelial cells. Other proteins under study include 9 ABC transporters previously described as virulence factosr that protect against the intranasal challenge with *S. pneumoniae* and induce opsonophagocytic antibodies [25] as well as two proteins ICSp1 and ICSp2 that are expressed during colonization and pneumococci infection [17].

Vaccines based on *S. pneumoniae* surface proteins could overcome the problems associated with capsular polysaccharide vaccines. Protein based vaccines are likely to be cheaper than conjugated polysaccharide vaccines, and proteins are often highly conserved between different *S. pneumoniae* strains protecting against several serotypes, thus preventing serotype replacement [17-19]. Moreover, these proteins can be used as carrier proteins in a conjugated vaccine eliciting protection against the remaining serotypes. Also, proteins stimulate T cell-dependent immune response that can evoke effective immunity in children as well as adults. The distribution of this vaccine to third world countries would become possible, thus reaching a broader target group then ever before.

The effect of vaccination on bacterial dynamics depends on the kind of protection that is elicited. When vaccination leads to the prevention of pneumococcal carriage, the horizontal spread of pneumococcal strains will also be diminished; this can protect unvaccinated individuals against pneumococcal diseases. On the other hand, this may also lead to susceptibility towards non-vaccine serotypes or genotypes and even alternative pathogenic species, and hence, disease burden. The vaccine should elicit a high level of cross-reactivity against the heterogeneous spectrum of subtypes to avoid the escape by recombination events. Several potential proteins display complex mosaic structures as a result of the horizontal (inter-species) exchange of gene parts. For

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this reason the protein vaccines requires studies in animal models before being applied on humans.

Advances towards animal models for Protein pneumococcal vaccine standardization

Several aspects have been discussed in order to raise a consensus regarding the most effective way to test potential pneumococcal vaccine candidates for selecting the best possible candidates to be used in human clinical trials. The discussion on the current experience with animal models in research and industry laboratories include 7 major topics such as: 1- Preferred animal species and strains, 2- Passive protection, 3- Challenge pneumococcal strains, 4- Route of pneumococcal challenge, 5- Positive protective controls, 6- Endpoints, 7- Correlates of Protection [26].

Preferred animal species and strains

Most participants favored the mouse, at least at the initial stages of screening for efficacy but less agreement was achieved on the mouse strain to be used. Other animals such as the chinchilla and rat have been used, since these animal models are only suited for the evaluation of pneumococcal otitis media. Furthermore, it does not seem likely that studies in non-human-primates (NHP) will be required before starting human trials unless specific safety issues justify these studies because of their high cost.

Passive protection

There was no consensus on the relevance of passive protection testing for protein candidates. Several protein vaccines elicited both, antibody and cellular immune responses, which provide partial or no correlation with protection during passive transfer experiments. Recently, it has been suggested that new mechanisms participate in the protection against pneumococcal colonization in an important way, such as those provided by CD4+T cell.

Challenge pneumococcal strains

Researchers are currently using a wide variety of pneumococcal strains but the aspects outlined as important criteria for strain selection in challenge experiments including:

▪ Strains that are epidemiologically important in humans and well studied in mice.

▪ Virulence in mice and reproduciblility of virulence over time.

▪ Human strains from developing countries and regions of interest.

▪ Strains infecting children under five years old.

▪ Opaque strains for intraperitoneal challenges.

▪ Transparent strains for colonization studies.

▪ Strains that have undergone limited subcultures and passages.

Route of pneumococcal challenge

Intranasal (IN), intraperitoneal (IP), and intravenous (IV) are the most frequent routes used to deliver *S. pneumoniae* in challenge experiments. Howerver, the main question is which route best mimics human diseases and predicts protection in humans. It is clear that the route chosen has to match an invasive or colonization model to meet vaccine characteristics. Six possible challenge routes including: aerosol, intranasal, intranasal with anesthesia, intratracheal, intraperitoneal, and intravenous. Although the methods and the use of anesthetics still needs to be standardized considering that different methods affect the way the pneumococci are brought into lungs.

Positive Protective Control

The ideal positive control for protection proposed was the currently licensed seven-valent conjugate vaccine since it is highly effective, but other controls could be used including the passive transfer of serum from subjects immunized with killed whole-cell vaccine or pneumococcal surface protein A (PspA) although none of the latter possibilities have a standardized production process.

Endpoints

In murine models of invasive pneumococccal diseases for candidate testing, common endpoints include time to death or to a morbid condition, percent survival and pneumococcal colony forming units (CFUs) in the blood and lungs. However, when evaluating colonization, the most important endpoint is nasal CFUs at five to seven days after the bacterial challenge. Because the different *S. pneumoniae* serotypes have varying growth curves, the endpoint should be standardized for the particular bacterial strain. The use of bioluminescent bacteria provides an advantageous strategy, since it generates images of disease localization and progression.

Correlates of Protection

Identifying and measuring serological correlates of protection for protein pneumococcal vaccines is still a challenge in the mouse model. Standard tools used to evaluate vaccines in humans include the opsonophagocytic assay (OPA) that can also be used in the mouse models, however, some antigens do not elicit opsonophagocitic antibodies, but induce protection in challenge models. Because of that, other assays were suggested as correlates of protection including:

▪ OPA (uptake assay)

▪ OPA-K (killing assay)

▪ ELISA (levels, isotypes, avidity)

▪ Cell culture binding assays (colonization and models)

▪ Passive Protection

▪ CD4+T cells analysis including Cytokine responses

▪ Cell adhesion/invasion inhibition

▪ Interference with the complement

Conclusions

The *S. pneumoniae* is still a human health problem worldwide, although, there has been much progress in understanding the pathogen-host ship relation, the identification of new virulence factors and the response of the immune system against this bacterium. Evidence is needed to clarify the key topics to improve vaccine development and control of pneumococcus infection: What are main differences between children in developing and developed countries, and how may this influence the selection

26. Animal Models for Proteins Pneumococcal vaccine Evaluation: meeting Summary; 2005 Nov 18 Held in Washington DC USA.

of vaccine candidates? What are the relevant immune response mechanisms in animal models of the invasive disease and in colonization? Can a protein pneumococcal vaccine be administered together with other routine childhood vaccines without any interference? In the meantime, the conjugate polysaccharide vaccine has achieved with undoubted an impact on pneumococcal control in countries where the vaccine has been introduced. New vaccine manufacturing facilities, especially in undeveloped countries, are needed to make the vaccine available to those who suffer more from the disease.