Protein and Other New Approaches to Vaccination Against *Streptococcus pneumoniae*

Current status and Research Needs

Seattle, November 27, 28, 2001

Meeting Report

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Introduction

Pneumonia and invasive pneumococcal disease are a major cause of childhood mortality, 90% of which occurs in developing countries. Routine childhood vaccination would be a cost-effective method for preventing this mortality. Pneumococcal polysaccharide (PPS) vaccines have been available since 1977 but are not immunogenic in infants and young children who comprise the largest proportion of those affected by pneumococcal disease. A 7-valent pneumococcal conjugate (PnC) vaccine was recently licensed in the US and it other developed countries. However, these vaccines cover only 40-70% of the serotypes causing invasive disease in developing countries in Asia and Africa. The next generation of PnC vaccines comprising of 9 or 11 serotypes are currently being evaluated in developing countries. While these vaccines would cover the majority (70-80%) of the invasive serotypes of pneumococcus in children world wide and initial results show that these are very safe and efficacious vaccines, there are a few unresolved issues related to these vaccines. The main technical problem is the potential for replacement disease with non-vaccine serotypes that may attenuate the overall benefit seen from reduction in disease due to vaccine serotypes. This phenomenon has been documented with otitis media in a trial in Finland, but not with invasive disease in the trial in Northern California. It is currently not known whether this would occur with pneumonia, the primary outcome of interest for developing countries. There are also several other concerns about the conjugate vaccines related to the cost and complexity of manufacture, and problems with registration of newer candidates in the United States. However, it is unclear whether these would be sufficient impediments to the introduction of these vaccines in developing countries.

The parallel development of alternate pneumococcal vaccine strategies offers the potential for extending the protective capabilities of conjugate vaccines by providing broader serotype coverage, which may also overcome the problem of serotype replacement, as well as the cover other high risk target groups who may not, be covered by the current conjugate vaccine formulations, e.g. the elderly.

NEWER VACCINES AGAINST PNEUMOCOCCUS

Pneumococcal proteins as vaccine candidates

There is considerable diversity among bacteria in their genomic structure. Moreover, there is a potential for change even within a bacterial species as a result of natural transformation or recombination. This diversity may translate into divergence in the surface proteins that are potential vaccine candidates.

Diversity among the protein antigens is an important consideration in selection of vaccine candidates. Many of the proteins required for critical bacterial functions show diversity among strains. However, they may offer cross-protection despite this diversity. To be

able to optimally use these proteins as vaccine antigens it is necessary to define the units of diversity and understand diversity generation.

Pneumococcal surface proteins that are currently being considered as potential antigens for vaccine formulations include: PspA, PspC, PsaA, and Pneumolysin (Ply), BVH-3 and BVH-11. Of these, PsaA, Ply, BVH-3 and BVH-11 are relatively non-variable antigens while PspA and PspC are variable, yet cross-reactive. Additional antigens may be identified by advanced genomics and reverse vaccinology. The characteristics of the most developed vaccine candidates are summarized in Table 1.

PspA and PspC

PspA is serologically variable yet cross-reactive. 95% of all tested strains fall into two families. Even though these families vary by about 40% in AA sequences, there was cross-protection against the other. Animal models have demonstrated protection against bacteremia/sepsis, pneumonia and nasopharyngeal carriage. Sera from humans and rhesus monkeys immunized with PspA protects mice against fatal challenge with a panel of different pneumococci. The protection works regardless of species in which the antibody in produced, including humans.

PspC or the related *Hic* proteins are present is all pneumococcal types. It seems to be involved in the pathogenesis of carriage, pneumonia and sepsis in animal models. Knock-out mutants without PspA and PspC are more attenuated than that deficient in each alone, suggesting complimentary activity in pathogenesis. Immunization with PspC protects mice against fatal sepsis.

PsaA

PspA is a membrane-associated, cell surface exposed, lipoprotein that is common to all serotypes of pneumococcus. It is immunogenic and in animal models has been shown to be protective against carriage when administered by the mucosal route. It has been cloned, sequenced and expressed. The recombinant protein is inexpensive to produce.

Antibodies to PsaA reduce but do not eliminate adherence to epithelial cells. Thus, there may be other adhesion molecules that play a role in adhesion of pneumococci to epithelial cells. It is not known whether this would result in some form of replacement phenomenon and this will need to be closely monitored in phase I/II human trials.

It is postulated that the reduction of carriage as a result of immunization with PsaA would result in reduction of pneumonia in adults, and otitis media in children. But a more suitable option would be to use this protein along with another protein that has demonstrated effect on pneumonia and invasive disease.

Pneumolysoid (PdB and PdBD)

Pneumolysin is a membrane damaging toxin from pneumococcus. This toxin is thought to play an important role in the pathogenesis of pneumococcal pneumonia.

PdB is a mutant form of pneumolysin that has only 0.1% of the hemolytic toxic activity of pneumolysin but retains 100% of complement activation activity. This is an effective immunogen. PdBD is another mutant that has 0% complement activation activity.

Ply, PdB and PdBD produce Ab response even without adjuvant but PdBD is less immunogenic. Repeated doses of PdB have not been associated with toxicity. In animal models immunization with PdB protects against lung inflammation caused by Ply and against pneumonia following challenge. It also protects against intraperitonial challenge, but not for all tested strains. The protection is cross-serotypic; with some strains there is no protection but the lack of protection is not serotype specific.

Combination of PdB, PspA and PsaA leads to a synergistic protective response in animal models of disease. Conjugation of Ply with 19F capsule also provides protective immunogenicity in an animal model that is greater than polysaccharide alone.

BVH-3 and BVH-11

BVH-3 and BVH-11 are ubiquitous, conserved, surface proteins of pneumococcus that are highly immunogenic in animals and show protective efficacy in mouse models. Both proteins have been well characterized and may be produced by recombinant technology. In animal models, they provide high levels of protection against pneumonia and sepsis. Phase 1 human trials of vaccines containing these antigens are planned.

Intranasal whole cell killed unencapsulated pneumococcus

Rx1AL is a strain of pneumococcus that is unencapsulated and also defective for autolysin. Killed organisms with cholera toxin as adjuvant when administered intranasally three times at weekly intervals induce protection against carriage, otitis media and pneumonia in animal models. The protection is cross-serotypic.

This approach to vaccination provides an inexpensive product that would be easy to manufacture and offers the advantage of being thermostable and easy to administer. However, protection against a variety of serotypes has not been demonstrated and the use of intranasal adjuvants in humans is controversial and may lead to difficulties in getting the product registered for human use. Currently, this technology is being developed by academic groups, without direct links to an industrial partner.

Intranasal whole cell killed encapsulated bacteria have been shown to provide protective efficacy against the same serotype in mice, even when administered without adjuvant. But it is not known if cross-serotypic protection would be obtained with this approach.

Other vaccine candidates

Several other protein antigens have undergone pre-clinical testing. They include *Pht* (Pneumococcal histidine triad) *Lyt* C (autolysin) *Cbp*A (choline binding protein), 29 kDa C3 protease, and *Php*A. All these candidates have shown protective efficacy in animal models. Phase 1 human trials are planned with some of these candidates.

Novel approaches to new vaccines

The recent advances in molecular biology and immunology provide further opportunities for developing newer vaccine formulations. These include the use of reverse vaccinology and expression libraries to quickly identify potential vaccine antigens,[1] [2] DNA shuffling, priming in neonatal period using BCG vectors, DNA vaccines[3] and boost with protein vaccines.

In addition to the development of newer vaccine candidate, the use of conjugate vaccine may be optimized by testing out newer vaccination schedules or by the use of newer adjuvants. Such efforts may require the creation of new infrastructure that promotes partnership between academia, biotechnology companies, vaccine manufacturers and multilateral agencies aimed at the targeted development of new vaccination approaches.

Conjugate Vaccines vs. protein vaccines: cost and complexity of manufacture

There was considerable debate whether the candidate vaccines were less complex to manufacture and whether this would translate into lower cost of vaccines. Opinion was divided on this issue and no consensus could be reached.

EVALUATING NEW VACCINES AGAINST PNEUMOCOCCUS

Natural Immunity

The leap from animal studies to human trials requires a demonstration that antibodies to pneumococcal proteins protect humans against disease. Studies on natural immunity may support the idea that vaccine will protect against disease. However, because vaccine

[1] Zysk G, et. al. Detection of 23 immunogenic pneumococcal proteins using convalescent-phase serum. Infect Immun 2000;68:3740-3.
[2] Wizemann TM, et. al. Use of whole genome approach to identify vaccine molecules affording protection against Streptococcus pneumoniae infection. Infect Immun 2001;69:1593-8.
[3] Miyaji EN, et. al. PsaA and PspA DNA vaccines induce humoral and cellular immune responses against Streptococcus pneumoniae. Vaccine 2002;20:805-12.

induced immunity may be better than natural immunity, these studies will not disprove the potential efficacy of vaccines.

Seroprevalence antibodies show that prevalence of anti-PspA and anti-Ply increase with age; anti-PspA prevalence increases only after 2 years of age. Anti-PsaA prevalence is approximately the same for all ages.

There is only a limited amount of data on natural immunity and protections against subsequent disease. Rise in anti-PsaA and anti-Ply are seen in adults with pneumococcal pneumonia; the rise was most evident in those with bacteraemic pneumonia. On the other hand, anti-PspA levels showed a 2-fold rise in only 15% of Finnish children with IPD. Observational studies in Filipino children did not support the notion that natural immunity protects against carriage or otitis. Thus, these observational studies do not provide convincing evidence that naturally acquired antibody to protein antigens protect against invasive disease or carriage. However, natural immunity studies are prone to epidemiological pitfalls. Further studies using methods to minimize these pitfalls may provide more useful information. These studies should be individual rather than community-based studies, avoid reverse causality, control for the effects of other risk factors and, if possible, be restricted to populations with little capsular antibody.

Animal models

In addition to providing pre-clinical data on the safety and efficacy of candidate vaccine, animal models can provide a better understanding about the pathogenesis of disease, may lead to the identification of immunological correlates of protection and define end points short of target organ efficacy that may be used in human trials.

There are several animal models that may be used to evaluate new pneumococcal vaccine candidates. Separate models are available to study carriage, otitis, pneumonia and sepsis. However, there is considerable variability in the susceptibility of different species to pneumococci. Susceptibility also varies depending on the strain of pneumococci used. Response to vaccines may also differ between species. Often, laboratories experience difficulty in reproducing a model that is successfully used in another laboratory. All these makes it difficult to standardize animal models across laboratories. Since the relevance to human protection of anti-protein antibodies showing protection in rodent models of pneumococcal disease is not clear, there may be role for a primate model to develop information with predictive validity in the prevention of invasive disease in humans. However, this model is likely to be difficult and expensive to develop.

Human colonization model

Human colonization models offer some benefits over the animal models since carriage is the first step in pathogenesis of pneumococcal disease one could surmise that prevention

of carriage would prevent disease in humans who are the only natural host for *S pneumoniae.*

A human colonization model has been used at Baylor College, Texas, using a type 23F and 6B clinical isolates in healthy adults. 6 of 14 subjects were colonized without any serious side effects. Susceptibility to colonization did not correlate to pre-existing anti-capsular antibody for 23F. All colonized subjects had antibody to an 22kDa antigen post colonization, whereas none of the non-colonized individuals had this antibody. On analysis the protein was found to be a truncated version of PspA from a mutation that caused a frame shift in the 23F isolate that was used. The protein fragment is in the hypervariable region of PspA. The non-colonized subjects had low levels of pre-existing anti-PspA whereas those who were colonized did not and they developed a high antibody to the protein after colonization. Antibody to no other proteins correlated to protection or susceptibility to carriage.

While these data suggest that full-length PspA expression is not stable, they suggest that immunity to PspA is effective even if only a N-terminal fragment of the protein is produced by the colonizing strain. Further research looks at the stability of the full length expression of PspA and also look at pattern of antibody responses to other potential candidate antigens. If pneumococcal strains with low invasive potential could be identified, a challenge model for human colonization could be developed to evaluate new vaccine candidates. However, the validity of these strains in predicting vaccine efficacy need to be carefully considered.

Target populations and outcomes for vaccine evaluation

Infants and young children are probably the highest risk group for pneumococcal disease worldwide. In some countries, the HIV epidemic has substantially increased the burden of disease. In developed countries pneumococcal pneumonia is a major cause of death in the elderly. Data from this age group is lacking in developing countries. The conjugate vaccine formulations that are licensed or under evaluation only cover only a limited number of the serotypes of pneumococcus that cause adult disease. Though the polysaccharide vaccine provides some benefit in this age group, protection is short-lived.

Among children in developing countries, pneumococcal pneumonia is the outcome that has greatest public health importance. A demonstrable impact on childhood mortality would be very useful for advocating for introduction of the vaccine in resource poor countries. However, this effect is difficult to measure, especially since easy access to medical care has to be provided in a trial and this in itself would reduce mortality. Sepsis, meningitis, otitis and antimicrobial resistance are other important target outcomes. However, these are less important in developing countries. Nasopharyngeal carriage is important to measure as it would provide information on herd effect and potential for serotype replacement.

In summary, based on available data, the main target population in developing countries for pneumococcal vaccination would be infants, young children and HIV infected individuals. In these populations, the main disease target is pneumonia and invasive disease. The elderly also represent an important target group in developed countries. More data is required from developing countries to determine the burden of disease in this age group.

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Pre-clinical evaluation

The objectives of pre-clinical testing would be to establish the safety, immunogenicity and efficacy of vaccine candidates in the laboratory prior to initiating clinical trials on human subjects. Pre-clinical evaluation may also contribute to the understanding of the role of the antigen in pathogenesis and what mechanisms the pneumococcus may have to escape the protective efficacy of antibody to specific antigens. The latter will be very useful for assessing probability of success.

The serological assays to measure the immune responses to conjugate vaccines are being standardized by a working group at the WHO. However, since the antigens are different in the protein vaccine candidates, serological assays would not be useful for comparing antigens. Protection in animal models may be used instead but standardization of animal models is very difficult but may be achievable. Each assay works differently in different labs. There are several antigens that have been evaluated in animal models and are ready to go into clinical trials. Identification of appropriate assays to test for efficacy against carriage, pneumonia, sepsis/meningitis and passive protection to compare available antigens or combinations of antigens would be useful in making decisions on which of these should be tested in clinical trials in humans. Since assays vary from lab to lab, reference labs where these assays may be conducted may need to be set up.

Clinical testing (Phase I/II)

The objectives of this phase of testing would include evaluation of:

1. Routes of administration
2. Monovalent vs. multivalent vaccines
3. Dose response
4. Immunization schedule
5. Formulations (adjuvants etc.)
6. Compatibility with concomitant vaccines
7. Effect on colonization
8. Correlates of protection

Phase I studies would ideally be conducted in healthy adults, with step-wise dose escalation using a open label or placebo controlled study design, measuring the reactogenicity and immune response to vaccination.

In phase II studies one would have to move in a step wise manner to the ultimate target group, i.e. infants. For multivalent vaccines, antibody response to the individual antigens as well as the efficacy of the combination in passive protection in animal challenge models may have to be studied. The study design should ideally 3 groups: protein, conjugate and placebo – sera can be used for passive protection studies in animal models or human colonization models.

Easiest functional assay is mouse protection. However, the challenge will be to identify the right model and conditions that would permit valid interpretation of the results. In current scenario, human challenge studies are more difficult to get through IRBs. However, using knock out strains that permit colonization but have lower pathogenic potential (e.g. pneumolysin deficient strains) may permit the use of human models in specific well-controlled settings.

Phase 3 clinical trials

Phase 3 trials of newer vaccines against pneumococcus would be required to demonstrate that the vaccine is safe and provides protection against invasive pneumococcal disease (IPD), radiological pneumonia and nasopharyngeal carriage. The options for evaluating a new vaccine with these objectives in mind would be to conduct trials in the elderly first and then scale them down to include infants and children. Ideally, the trials in infants and children should be randomized clinical trials (RCTs) comparing the newer vaccines against placebo, conjugate vaccine or both (i.e. a 3-arm trial). The other less ideal options would be open studies using a step-wedge or case-control design.

Phase 3 clinical trials of new vaccines against pneumococcus in a RCT will be a challenge with conjugate vaccines being licensed and available in many countries around the world. This would mean that RCTs of a newer vaccine would need to show equivalence to the existing conjugate vaccine. Such trials would be very large and expensive to conduct if bacteriological outcomes were used as the primary end point. Studies with radiological pneumonia and carriage may be possible with smaller sample size, but the results would be difficult to interpret. The current iteration of the Declaration of Helsinki is very stringent regarding the use of placebos in clinical trials. Even the recent clarification published by WMA requires that very sound scientific and methodological reasons be provided to justify the use of placebos and that their use should only be for conditions where serious harm will not occur to the placebo recipient. In this scenario, obtaining ethical approval for the use of placebo in the control arm would become increasingly difficult.

Alternatives to RCTs would be to conduct pre-licensure case-control studies or effectiveness studies using a step-wedge design in countries where conjugate vaccines are not part of routine immunization. Alternatively, there are sites where the epidemiology of disease has been intensely studied and the baseline has been consistent over a period of time. In such sites, impact on this disease incidence would be a better design. The

problem with this design is that there is no control for safety. None of these study designs are optimal.

A narrow window of opportunity still exists for the evaluation of new vaccines in placebo controlled clinical trials. While none of the current manufacturers of alternate vaccines against pneumococcus have firm plans for phase 3 trials of their vaccines, they will undoubtedly make such plans once clinical testing has proceeded beyond the initial Phase 1 trials. Decisions would be based, in part on risk assessment and ability to support multiple major development programs.

The role of Public sector in getting reasonably sound estimates of the disease burden in developing countries and building capacity in developing countries for conducting phase 3 trials would be very useful in promoting the evaluation of new vaccines.

SPECIAL ISSUES RELATED TO THE DEVELOPMENT OF NEW VACCINES AGAINST PNEUMOCOCCUS

Regulatory Issues

The regulatory issues related to new vaccines depend on a number of factors. These include: (1) whether the vaccines are meant for universal use or whether different vaccines will be used for developed and developing countries; (2) whether introduction will be simultaneous in developed and developing countries or whether it will continue to be the trickle down introduction that occurs currently; (3) whether there will be one or multiple formulation/presentation.

WHO is currently reviewing several regulatory pathways that may allow use of new vaccines in developing countries. These include:

- Licensing in country of manufacture
- Orphan product
- Shared manufacture and licensing by filler
- Export to listed countries
- Pseudo-licensing for WHO

None of the above assure day-to-day regulatory oversight. Also, they do not assure epidemiological appropriateness of the vaccine in another country. For the latter, there are plans to establish Regional Advisory Groups to come up with suitable recommendations.

Transfer of technology may be one way of assuring supply of vaccines for use in developing countries at affordable prices. However, this requires the presence of a viable national regulatory authority (NRA) and a proper understanding on GMP. Experience has

shown that joint ventures between developed and developing country manufacturers is a better option. There is precedent for doing this with combination vaccines with components from different companies.

IP Issues

New vaccines will not be successfully commercialized unless we deal with intellectual property (IP) issues at the outset. Though the process of mapping the patent landscape may appear very complex and appear to be an insurmountable barrier, it can in fact be used to orchestrate the various players to move forward with a particular combination product. The present patent landscape for the protein antigens are not as complex as many other vaccines. The problem with protein vaccine antigens is not so much with public sector agencies holding patents but in how the licensing of the product is done that may be detrimental to making the product available for developing countries.

Safety issues with intranasal immunization

In animal studies, use of potent intranasal adjuvants such as cholera toxin and LT have been shown to be able to cross cribriform plate and cause severe lesions in respiratory and olfactory mucosa, inflammation of meninges, olfactory nerves and glomerular layer of olfactory bulb.

However, clinical safety studies with intranasal administration of Cholera toxin B (CTB) showed no visible effects on nasal mucosa and no systemic adverse events or long term sequelae. The only adverse effects seen were sneezing, nasal itching, neck spasms and ear and face pain. Low doses of LT mutant also showed only similar minor adverse effects in humans.

At a recent meeting on the subject held at NIH, it was decided that the potential adverse effects of newer adjuvants, especially those containing toxins and their mutants should be carefully studied because of their ability to attach to GM1 receptors on olfactory nerve endings. A number of recommendations were made that should be taken into consideration when evaluating vaccines for intranasal preparations (ref to NIH document)

STEPS TO ACCELERATE THE DEVELOPMENT OF NEW VACCINES AGAINST PNEUMOCOCCUS

Lessons from the Malaria Vaccine Initiative

Though there are many differences between pneumococcal disease and malaria, there are several lessons from the Malaria Vaccine Initiative (MVI) that may be useful in the development of new vaccine against pneumococcus.

As with the MVI, the focus with new vaccines against pneumococcus should be on development rather than or discovery or core development of platform technology. Public sector input will be required for vaccine candidates that are tailored to meet developing country requirement that may not represent a market for private industry. It needs the co-ordinated activity of a number of diverse partners, including academia, biotech companies, vaccine manufacturers, and developing country investigators, which in turn requires an understanding of the culture and the language of the partners.

There are a number of factors that need to be taken into consideration while developing a vaccine development project. These include:

1. Is there a credible prioritization of vaccine and or strategy?
2. Are there defined and agreed upon targets?
3. Are the barriers defined?
4. Can industry do this alone, could partnership accelerate or expand the plans?
5. Is there a strategy for ensuring access to the developing world?

Finally, it is useful to remember that a program depends heavily on probability of success rather than return of investment.

ACTION PLAN FOR THE DEVELOPMENT OF ALTERNATIVE VACCINES AGAINST PNEUMOCOCCUS

Objectives:

- Identify specific activities related to development of protein and other new vaccines against pneumococcus that would benefit from public sector involvement.
- Integrate these activities into the pneumococcal conjugate agenda to make a comprehensive pneumococcal vaccine agenda. This step helps to minimize redundancy of efforts and to coordinate overlapping activities (e.g., disease burden).
- Craft a message that development of protein vaccines is not predicated on the failure of conjugate vaccines, but that the two may be done in parallel and that the protective benefits of each may be complementary to the other.

  e.g. accelerate the development of alternate vaccines in order to extend the protection of the pneumococcal conjugate vaccines beyond the existing serotypes and to other at-risk populations.

Suggested Activities

A. One-on-one discussion with industry to ascertain their development plans (who? what? when?) and then compare what industry is planning to do without public sector involvement with what public sector would like to see happen. The difference serves as the basis for possible public sector input.

Are they willing for partnership?
Are they willing to commit to tiered pricing?
What are their timelines?
How do we present the project to them. and who conducts the visits?

B. Develop criteria to select candidates that would go into public sector funded human trials:

- Define the performance characteristics of the vaccine and target outcomes vis-a-vis, prevention of colonization, otitis, pneumonia or invasive disease
- Define the appropriate models to test for efficacy against carriage, otitis, pneumonia and sepsis
- Establish reference laboratories where such assays may be conducted. E.g. for head-to-head comparison of candidate antigens.

C. Support phase II and phase III trials of candidate vaccines with the most favourable characteristics in a target population in a developing country that address outcomes of public health interest to those countries, using schedules and are compatible with routine infant immunization.

- Develop criteria to select potential trial sites
- Prepare trial sites for phase 2/3 trials.
- Discussions with decision-makers on the number of efficacy trials that may be required for widespread uptake of the vaccine.

D. Develop a plan to raise funds and find partners to carry out the activity.

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Protein Vaccines and Other New Approaches to Vaccination Against *Streptococcus Pneumoniae*

Current Status and Research Needs

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Table 1. Status of alternate pneumococcal vaccines

Vaccine candidate	Developer	licensee	Bacteremia protection	Pneumonia protection	Carriage protection	Cross-capsular Serotype protection	human studies	other comments
PspA	UAB	Aventis	++	++	+	+	Phase 1	Passive protection with human antibody
PspC	?	?	+		++	+	No	
PsaA	CDC	Aventis	-	-	++	+	No	
PdB	Paton, Andrew	RIVM	+	++	-	+	No	
PspA+PsaA+PdB	Various	Various	+++	+++	++	++	No	
BVH-3 & 11	Shire	Shire	++	++	?	+	No	
IN whole bacteria								
Unencapsulated	Anderson	None	+/-	+	++	+	No	Adjuvanted with CT
Encapsulated	Haneberg		+	?	?	No	No	

Protein Vaccines and Other New Approaches to Vaccination Against *Streptococcus Pneumoniae*

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Protein Vaccines and Other New Approaches to Vaccination Against *Streptococcus Pneumoniae*

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Tuesday, November 27 — **Silver Cloud Inn**

8:00 – 8:30 AM	Materials pick-up	
8:30 – 8:45 AM	Welcome and Introductions	T. Aguado J. Maynard M. Liu
8:45 - 9:00 AM	Meeting Goals and Objectives	M. Steinhoff
Tab A		
9:00 – 9:30 AM	Distribution of Antigens in Pneumococcal Strains	S. Hollingshead
Tab B		
9:30 - 10:00 AM	**Candidate Antigens: Current Status** PspA/PspC	D. Briles
10:00 – 10:15	Break	
10:15 – 10:45	**Candidate Antigens: Current Status (cont'd)** PsaA	E. Ades
Tab C		
10:45 – 11:15 AM	Pneumolysoid	P. Andrew
Tab D		

11:15 – 11:45 AM	Intranasal Killed and Attenuated Organisms	P. Anderson
Tab E		
	Natural Immunity to Common Protein Antigens	
11:45 – 12:15 PM	Invasive Disease	A. Scott
12:15 – 12:45 PM	Carriage and Otitis	H. Käyhty
12:45 – 1:45 PM	Lunch	
1:45 – 2:15 PM	Intellectual Property (IP) Issues Relating to Common Protein Antigens	G. Galloway
Tab F		
2:15 – 2:45 PM	Summary (including discussion of other potential antigens and combinations)	R. Insel
2:45 – 3:15 PM	Animal Models	S. Giebink
3:15 – 3:30 PM	Break	
Tab G		
3:30 – 4:00 PM	Human Pneumococcal Colonization Model	J. Weiser
4:00 – 4:30 PM	Safety Issues with Intranasal Vaccines	D. Klein
4:30 – 5:45 PM	Pathway for Vaccine Development – Industry	

	Perspective Aventis Glaxo SmithKline Shire Biologics Wyeth-Lederle	
6:30 – 8:30 PM	Dinner hosted by Gates Foundation	

Wednesday, November 28 **Silver Cloud Inn**

Tab H

8:30 – 9:00 AM	Target Populations and Outcomes Discussion: Issues in Selection and Evaluation of Vaccine Candidates	C. Whitney
9:00 – 9:30 AM	The Malaria Vaccine Initiative and Meningitis Vaccine Program – Lessons Learned in Public/Private Vaccine Development Partnerships	R Rabinovich

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9:30 – 10:00 AM	Preclinical Testing Models Outcomes	R. Rabinovich
10:00 – 10:15 AM	Break	
10:15-10:45 AM	Preclinical Testing Discussion	
10:45 – 11:30 PM	Clinical Testing Safety Immunogenicity	M. Levine
11:30 – 12:15 PM	Clinical Testing Protection Ethical Considerations	K. Mulholland
12:15 – 1:15 PM	Lunch	
1:15 – 2:15 PM	Regulatory and Licensing Issues	J. Milstien

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2:15 – 3:30 PM	Open discussion with all participants – Accelerating the Pace of Vaccine Development; Financing; Partnerships	M. Steinhoff
3:30 – 4:00	Break	
4:00 – 5:00 PM	Summary and Next Steps	O. Levine R. Spiegel
5:00 PM	Adjourn	