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Group A streptococcal vaccine development: current status and issues of relevance to less developed countries

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Executive summary

In light of the current lack of a clear strategy for primary prevention of GAS infections, there is definitely a place for a safe, effective, affordable and practical GAS vaccine. Based on the epidemiology of GAS diseases in less developed countries, there is some concern that the vaccine most advanced in development – a multivalent, type-specific vaccine – may not provide sufficient and long-lasting protection in countries with highly endemic GAS diseases. As a minimum, the efficacy of this and other GAS vaccines should be assessed in less developed country settings prior to advocating their widespread use. There is an urgent need for oversight and coordination of GAS vaccine development on a global scale. The priorities must be to ensure that a vaccine becomes available specifically for the prevention of GAS diseases in less developed countries, that any vaccines are therefore tested for safety and efficacy in less developed countries (or similar settings) using ARF, APSGN and skin infections as primary endpoints, and that preparations begin now for compiling important regional disease burden data that will be used in making decisions about introducing a GAS vaccine.

AN ACTION PLAN FOR GAS VACCINE DEVELOPMENT

Collaboration and coordination

Presently each research group operates independently, without much evidence of collaboration between groups. The progress of a number of the candidate vaccines is not known. WHO, NIH, and GAVI are the 3 organisations best placed to influence the process.

A meeting of experts

This meeting should include experts in GAS vaccines, epidemiology and control, and in vaccine development in general. The aims of the meeting would be to:

- provide updates on the current status of each candidate vaccine.
- identify obstacles that each group is facing.
- clarify the target groups for each vaccine; i.e. what disease(s) is the vaccine being primarily aimed at preventing, at what age will it be administered, and in what geographic region(s)?
- discuss the likelihood of each vaccine being efficacious, affordable and available for the prevention of the most important GAS diseases in developing countries (i.e. ARF, APSGN, invasive disease).
- determine the level of planning for downstream clinical trials of each vaccine; i.e. what immunological, safety and disease endpoints will be used, and in what population(s)?
- conduct a global discussion about GAS vaccines, including target groups for vaccination, obstacles and downstream clinical trials.
- clarify the regulatory and licensing issues involved for GAS vaccines.
- determine whether current understanding of immunological correlates of protection is sufficient, and if appropriate animal models of GAS diseases exist.
- consider if new vaccine antigens, adjuvants or modes of antigen presentation may be needed.

- discuss possible collaborations between research groups, including combinations of different vaccine antigens, adjuvants and/or modes of antigen presentation.
- determine the role and interest of the pharmaceutical industry in GAS vaccines, and ensure that industry is aware of the true public health role of a future GAS vaccine and the endpoints against which it should be assessed.
- discuss possible ways in which groups like WHO, GAVI, NIH and others may improve the likelihood that a GAS vaccine may become available that is of proven efficacy against the major GAS diseases in less developed country settings.

Preparation of key field sites

This is linked to the findings of the separate disease burden review compiled as part of this same consultancy, in which it was recommended that field sites be established for GAS disease burden studies in less developed countries. Any of these sites may then be suitable for clinical trials of GAS vaccines. The most critical requirement is that each new vaccine have at least one high-quality efficacy trial using ARF and APSGN as primary endpoints.

Further activities

- The meeting of experts will hopefully identify a list of other priority research questions and other activities for attention.
- In view of the orphan status of GAS vaccine development, there will be an important role for advocacy with funding bodies, industry, GAVI, governments and other organisations.
- There is a clear need for ongoing oversight of GAS vaccine development, to ensure that the needs of the less developed country market are always being catered for.

Introduction

This document will not present a comprehensive overview of GAS vaccine development. A number of reviews have been prepared on this topic, and the reader is referred to the following references. (1-8) Moreover, a chapter about GAS vaccine development co-authored by Drs Good, Cleary, Dale, Fischetti, Fuchs, Savharwal, and Zabriskie will soon be published in a new edition of "New Generation Vaccines", edited by Dr Mike Levine. This will be a valuable reference on this topic. Instead, this review will briefly summarise the current status of efforts to develop a GAS vaccine, and highlight important issues relating to the potential for a vaccine to become available for use in less developed countries.

Antibodies directed against the surface M protein of GAS are able to opsonize and lead to phagocytic clearance of GAS. (9) This antibody response is type-specific; it is directed against the hyper-variable amino terminal region of the streptococcal M protein, and protects against only GAS organisms of the same M serotype. (10, 11) The antibody response has been demonstrated to persist up to 32 years in some individuals, but in others there appears to be no persistent protective response. (12) The persistence of type-specific antibodies is not correlated with the severity of the initial infection or the GAS serotype. (12) These type-specific anti-M protein antibodies have been considered by many to be the basis for passive protective immunity from GAS infection, although others argue that antibodies to the conserved region of the M protein or to GAS carbohydrate may be more important for passive immunity. (13-15)

Because it may be the target of naturally-occurring protective immune responses, confers protection to GAS against complement-mediated phagocytosis, and is considered to be the main virulence factor of GAS, (4, 16, 17) the M protein has also been considered a major candidate for a GAS vaccine. M protein-based approaches fall into two categories: those based on type-specific epitopes present at the amino terminal of the protein, and those based on epitopes conserved among all or most GAS strains, present in the C-repeat region towards the carboxy terminal of the protein.

However, not all vaccine candidates are based on M protein antigens. A number of groups are working with GAS antigens other than M protein for two reasons. The first reason is that these antigens are conserved among all GAS strains, so it may be possible to develop a vaccine against all GAS rather than a limited number of serotypes (the same argument used by those working on conserved M protein antigens). The second relates to the safety of GAS vaccines. The M protein has long been considered to harbour epitopes that cross-react with human tissues and therefore are the basis for the autoimmune response seen in ARF. By avoiding M protein antigens entirely, these groups argue that they avoid the possibility of a vaccine inducing ARF, or sensitising vaccinees to later ARF.

These two issues, vaccine safety and type-specific versus non type-specific protection, require some further attention:

Vaccine safety

A report from 1969 described the administration of a vaccine made of partially purified type 3 M protein to 21 healthy siblings of ARF patients. (18) During follow-up, there were 18 proven GAS infections (none due to type 3),

and following GAS infections two vaccinees developed definite ARF and one developed probable ARF. The authors contrasted this rate with the much lower incidence of 5 cases of ARF following 447 streptococcal infections in unimmunised siblings. This study raised the possibility that a GAS vaccine may have the potential to predispose recipients to developing ARF following subsequent GAS infections. There is considerable doubt that the vaccine played a role in the ARF cases described by Massell, and there have been many other people immunised with M protein-containing GAS vaccines with no other cases of ARF described. Regardless, it is now incumbent on researchers developing GAS vaccines to seek antigens that have minimal chance of inducing immunological cross-reactivity, and to prove the safety of candidate vaccines in as many ways as possible. The US FDA will require extensive in vitro and animal data to prove absence of potential cross-reactivity before sanctioning human studies. During clinical trials, participants will need intensive screening for development of cross-reactive antibodies, and echocardiography to detect the appearance of subclinical carditis.

Type specific versus non-type specific protection

The amino terminal of the M protein is highly variable and frequently undergoes genetic recombination that can lead to loss in opsonizing ability of type-specific antibodies. (19, 20) In populations with high prevalence of GAS infection and carriage, there is very rapid turnover of GAS strains. In one small Australian Aboriginal community of only 250 people, GAS strains belonging to 31 different *emm* types were isolated over a 25-month period, (21) up to 11 different types were present at any one time, and almost all *emm* types present at the start of the study had been replaced by others 2 years later. Over the past 10 years, almost 100 different Vir types (closely linked to *emm* type) have been isolated from Aboriginal people in the Top End of the Northern Territory of Australia (Personal communication, B Currie). Even if a multivalent, type-specific GAS vaccine could be developed that offered protection against such an enormous number of *emm* types, the ecological pressure induced by introduction of the vaccine may promote the emergence of new *emm* types. The ability of the N terminal region of the M protein to vary its antigenic characteristics was demonstrated with *emm* sequence typing of 53 GAS isolates from northern Thailand, which revealed 13 previously uncharacterised *emm* types and a wide variety of point mutations, small deletions, and insertions in the hypervariable region compared to published *emm* sequences. (22) Even in affluent, temperate climate populations there is rapid turnover of GAS serotypes. In one community in the USA, the predominant M serotype causing pharyngitis changed completely within a 12-month period, in the absence of any known precipitant. (23)

A recent study of GAS isolates from Aboriginal Australians gave some hope to the multivalent N-terminal vaccine strategy. Thirty-nine N terminal peptides were raised from GAS isolates endemic in this population, which induced opsonic antibodies in mice after covalent linkage to tetanus toxoid and the addition of complete Freund's adjuvant.