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Review

Clinical development strategy for a candidate group A streptococcal vaccine

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ABSTRACT

Group A streptococci (GAS) cause a wide spectrum of diseases ranging from benign pharyngitis and skin infections to severe invasive disease and the immune sequelae rheumatic fever and rheumatic heart disease. Pharyngitis, one of the most frequent diseases caused by GAS, is highly prevalent in school-age children in temperate climates and a major cause of antibiotic use. An efficacious vaccine would reduce disease burden associated with pharyngitis and the need of care for sick children. Importantly, GAS pharyngitis is recognised as the main precursor for acute rheumatic fever so a vaccine that is efficacious against GAS pharyngitis should also prevent acute rheumatic fever and rheumatic heart disease. It may also prevent post-streptococcal glomerulonephritis and invasive disease since GAS pharyngitis is one of the precursors for these clinical syndromes. There has been no clearly articulated pathway for clinical trial design leading to GAS vaccine registration. This review outlines a clinical development strategy detailing the phases of development required for registration of a candidate GAS vaccine for GAS pharyngitis initially, followed by impetigo and associated sequelae. The major advantages of a strategy first focused on GAS pharyngitis is an early proof of principle, that can be followed by studies for other clinical syndromes. The end goal being the availability of a preventive tool for the most prevalent GAS-associated diseases globally.

Contents

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1. Introduction

Infection with the Gram positive bacteria *Streptococcus pyogenes* (group A *Streptococcus*, GAS) results in a wide range of disease and is a significant cause of morbidity and mortality. Disease ranges from superficial infections such as pharyngitis, skin infections and cellulitis to severe invasive disease including puerperal sepsis, necrotising fasciitis and streptococcal toxic shock syndrome. Secondary, post-streptococcal immune-mediated sequelae include acute glomerulonephritis and acute rheumatic fever (ARF). Rheumatic heart disease (RHD) can develop after one or more episodes of ARF and this structural heart disease frequently requires open heart surgery, and is often complicated by heart failure and premature death [1].

There has been no reduction in the global burden of GAS disease over recent decades, despite the bacteria remaining susceptible to penicillin. In 2005, it was estimated that the worldwide prevalence of severe GAS disease was approximately 18.1 million cases, with an incidence of 1.78 million new cases per year [2]. While invasive disease is a significant contributor to morbidity and mortality, by far the largest burden of GAS disease is associated with RHD. The 2010 Global Burden of Disease report estimated at least 34.2 million people were living with RHD resulting in at least 345,110 annual deaths [3]. Nearly all of these deaths occurred in low- and middle-income countries.

Though ARF is now rare in most resource-rich countries, considerable disease burden is observed in Indigenous populations in Australia and New Zealand. Australia's Aboriginal population experience one of the highest rates of ARF in the world – the incidence in Aboriginal children aged 5–14 years in the Northern Territories is 150–380 per 100,000 [4]. In New Zealand, rates for the same age group for Māori and Pacific Island children were reported to be 40.2 and 81.2 per 100,000, respectively in 2012 [5]. It was these concerning rates of ARF that led the governments of Australia and New Zealand to support the Coalition to Advance New Vaccines for Group A *Streptococcus* (CANVAS). This initiative was established to aid the development of GAS vaccines for Australia, New Zealand and other regions with high GAS disease burden.

Vaccination is the most practical strategy to reduce global GAS-associated disease burden in the long term. While timely treatment of pharyngitis can prevent ARF, such primary prevention strategies require very high coverage to be effective and are resource-intensive methods for controlling ARF at a population level [6]. Furthermore, GAS pyoderma has been hypothesised to play a role in ARF pathogenesis, particularly in tropical settings such as the Northern Territory of Australia and Fiji, where the incidence of GAS pyoderma has been reported to be as high as 80 per 100 child years [7–9]. If GAS skin infections are a precursor to ARF in some settings, this further limits the value of penicillin treatment of pharyngitis for ARF control. Vaccination would circumvent the challenges of antibiotic treatment adherence and would require fewer resources for implementation compared to primary prevention.

Vaccination will likely also reduce the increasing rates of invasive GAS disease [1]. Though the greatest burden of invasive GAS disease is found in low- and middle-income countries, it is also a significant problem in selected populations in high-income countries. This includes those living in areas of social deprivation within high-income countries and those with co-morbidities. Particularly concerning is the increased risk of invasive GAS disease in those with obesity and diabetes identified in recent studies from the USA and New Zealand [10,11].

There has been no clearly articulated pathway for clinical trial design leading to GAS vaccine registration. In this review, CANVAS provides a generic clinical development strategy detailing the clinical trial design and phases of development required for registration of a candidate GAS vaccine for GAS pharyngitis, impetigo and associated sequelae (Fig. 1). If broadly used, vaccines efficacious against GAS pharyngitis or impetigo should prevent ARF and serious invasive diseases.

GAS vaccines have been described as "impeded vaccines" [12] with vaccine development hampered by a number of factors. These include the complex epidemiology of GAS disease, a lack of surrogate markers for immune protection in humans, a lack of robust animal models and perceived safety concerns. The latter is based on a theoretical risk that GAS vaccines could lead to the development of ARF, despite all contemporary GAS vaccines under development having been designed to negate this risk. Perhaps the most significant hurdle in development is the fact that the most serious GAS diseases are primarily distributed in resource-poor settings. This, combined with their delayed onset and relative scarcity, has turned investors away from funding efficacy trials for GAS vaccines. The strategy outlined here (Fig. 1) leads, in the first instance, to the development of a vaccine for GAS pharyngitis – a high-incidence disease, distributed globally and responsible for wide-spread antibiotic use [2]. Prevention of GAS pharyngitis would provide proof of concept for efficacy and pave the way for the development of a vaccine with preventative uses in both resource-rich and resource-poor settings.

2. GAS vaccine antigens

The leading GAS vaccines are based on the M protein, encoded by the *emm*-gene. One of the difficulties in the development of GAS vaccines has been the diversity of GAS *emm*-types [13]. Added to this difficulty is the difference in *emm*-type distribution by geography and disease spectrum. The major circulating strains causing GAS pharyngitis in high-income countries differ substantially from

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