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Review

Group B streptococcal epidemiology and vaccine needs in developed countries

Pierrette Melin[a,*], Androulla Efstratiou[b,1]

[a] National Reference Centre for Group B Streptococci, Medical Microbiology Department, University Hospital of Liege, Sart Tilman, B-23, 4000 Liege, Belgium
[b] WHO Global Collaborating Centre for Diphtheria and Streptococcal Infections, Microbiology Services Division, Public Health England, 61 Colindale Avenue, London NW9 5EQ, United Kingdom

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ABSTRACT

Development of a group B streptococcal vaccine (GBS) vaccine is the most promising approach for the prevention of GBS infections in babies, given the potential adverse effects of intrapartum antibiotic prophylaxis as well as the need for effective prevention of both adult and late perinatal disease. There are numerous prevention strategies at this time but none are 100% effective in the eradication of neonatal early onset GBS disease and there are no preventative strategies for late onset disease. The need for a GBS vaccine is therefore, of utmost importance. Efforts applying genomics to GBS vaccine development have led to the identification of novel vaccine candidates. The publication of GBS whole genomes coupled with new technologies including multigenome screening and bioinformatics has also allowed researchers to overcome the serotype limitation of earlier vaccine preparations in the search of a universal effective vaccine against GBS. This review brings together the key arguments concerning the potential need of a GBS vaccine in developed countries and describes the current status with GBS epidemiology and microbiology in these countries.

Contents

* Corresponding author. Tel.: +32 4 366 24 38/39; fax: +32 4 366 24 40.
E-mail addresses: Pierrette.Melin@chu.ulg.ac.be (P. Melin), Androulla.efstratiou@phe.gov.uk (A. Efstratiou).
[1] Tel.: +44 20 8327 7270; fax: +44 20 8205 6528.

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1. Introduction

Emerging abruptly in the 1970s as an important life-threatening pathogen in neonates causing severe invasive bacterial infections, *Streptococcus agalactiae*, also referred to as Lancefield group B streptococcus (GBS) has become a notable global problem [1]. GBS has therefore, remained as a leading cause of neonatal morbidity and mortality in North America, Australia and Europe, affecting 0.5–2.0 neonates per 1000 live births [2–9]. Two distinct clinical syndromes are identified amongst infants according to their age at onset: early onset disease (EOD) presenting with mainly sepsis during the first week of life (0–6 days), and late onset disease (LOD) affecting infants between one week and three months old (7–90 days), with bacteremia and/or meningitis [1–5,10]. In EOD, GBS is transmitted from colonized mothers to the neonate during or just before birth. In industrialized countries, the rate of GBS early onset sepsis reached 3 per 1000 live births, with a mortality rate of 40% from the late 1970s to mid 1990s. From the 1990s to the present, where guidelines for prevention of perinatal GBS disease have been widely implemented, the incidence of neonatal EOD has dramatically decreased to <0.5 cases per 1000 live births but has not been eradicated and continues to be an important cause of neonatal sepsis and meningitis [4,8,9,11–16]. Because many babies with GBS EOD are already septicaemic at birth and thus limiting the opportunity for timely interventions, disease prevention rather than treatment has been the focus of attempts to reduce neonatal GBS infections and disease burden. Selective intravenous antimicrobial prophylaxis with β-lactams administered during labour and delivery to women who are colonized by GBS appears to be the most practical and effective mode of prevention of GBS EOD at this time. The main goal is to reduce or eliminate vertical transmission of GBS to the infant and the risk of perinatal sepsis [2,4,6,8,12]. Since their implementation and evolution, specific policies for intrapartum antimicrobial prophylaxis have significantly influenced the dramatic decrease of the overall GBS EOD incidence [4,9,11–13]. However, prevention of EOD is still subject to much controversy; there has been no consensus amongst European countries, and despite considerable efforts and economic resources spent on prevention of GBS-EOD, cases continue to occur in industrialized countries [1,3,5,6,11,17–19]. Furthermore, none of the strategies of intrapartum antimicrobial prophylaxis for "at risk" pregnant women have any effect on GBS LOD [8,20–22]. New improvements for the current prevention for GBS EOD are urgently required and an alternative strategy for prevention of both GBS early and late onset diseases is still long-awaited.

At the end of the 1970s, Baker and Kasper reported upon the existing correlation of maternal antibody deficiency leading to increased susceptibility to neonatal GBS infection [23]. Therefore, vaccination represented a practical, attractive alternative, targeting women of childbearing age to subsequently protect neonates against GBS EOD or LOD. In 2013, this perspective, which is finally approaching, raises numerous questions. What vaccine type will meet the expectations, a capsule based 3-valent or 5-valent vaccine conjugated or not to specific proteins such as pili? Will a future vaccine replace the current standard of care prophylaxis? What specific surveillance studies are required to establish the pre and post introduction of GBS vaccination for evaluating the impact on colonization, on potential serotype(s) replacement and on GBS resistance to antimicrobial agents? Are there other target populations for such a vaccine as GBS diseases are not restricted to neonates? Indeed, GBS are also common pathogens in pregnant women and are recognized as an ever-growing cause of severe invasive infections in non-pregnant adults, especially amongst the elderly and patients with underlying medical disorders [1,2,4,8,24].

The following review brings together the key arguments concerning the potential need of a GBS vaccine in developed countries.

2. Description of the bacteria and virulence factors

GBS, Gram-positive encapsulated cocci occurring in pairs or short chains, share a common antigen, the Lancefield group B polysaccharide antigen and are further distinguished on the basis of their type-specific capsular polysaccharides (CPS) into ten antigenically unique types (Ia, Ib, II-IX) [2]. The capsule represents one of the major GBS virulence factors, which helps bacterial evasion by interfering with phagocytic clearance except in the presence of type specific opsonophagocytic antibodies [2,10]. A small proportion of "non-typable" strains have also been isolated, currently accounting for 1% of isolates from invasive neonatal infection to 8% of colonizing isolates [25]. On blood agar, GBS colonies are surrounded by a narrow zone of β-hemolysis, however 1–3% of isolates are non-hemolytic. GBS β-hemolysin causes damage to lung microvascular endothelial cells and may contribute to the pathogenesis in EO GBS pneumonia [10,26]. This process may allow the bacteria to gain entry into the bloodstream [10]. All β-hemolytic isolates produce a red-orange pigment, granadaene when cultured under certain conditions [27]. Further differentiation is based upon the presence of surface proteins designated as C, R, X and Rib protein. Another important protein is the surface immunogenic protein (Sip) which is shared by all GBS isolates [28]. Recently, three variant cell surface-exposed filamentous proteins constituting pilus-like structures have been described [29]. GBS pili are composed of three subunits: a backbone pilin protein and two ancillary proteins, a pilus-associated adhesin and a component that anchors the pili to the cell wall. These are encoded by two loci in different regions of the genome, designated pilus islands 1 and 2 (PI-1 and PI-2), the latter presenting two distinct variants, PI-2a and PI-2b. Margarit and co-workers found that all strains of GBS carried at least one or a combination of the three pilus components [30]. These pili are presumed to be important virulence factors, as they appear to play a key role in the specific adherence of GBS to the host epithelial cells and promote transepithelial migration [31,32]. GBS produce other identified factors that interfere with host defenses, such as C5a peptidase that inactivates human complement component C5a, an important neutrophil chemoattractant [10]. Furthermore, cell wall components, such as lipoproteins anchored in the cytoplasmic membrane and lipoteichoic acid, trigger the host's inflammatory response that can induce a sepsis syndrome by activating immune cells via Toll-like receptor TLR2 [10,33].