REVIEW

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A Review of Current Knowledge on the Development of a Group B Streptococcus Vaccine for Pregnant Women and the Protection of Neonates: Advances in Diagnosis and Treatment

Akylas GRAMMENIATIS[a], Angeliki Rothi BURRIEL[b], Kalliopi PAPPA[c], Anastasios IOANNIDIS[b]

[a]Department of Obstetrics and Gynaecology, Royal Free Hospital NHS Foundation Trust, London, United Kingdom
[b]Department of Nursing, School of Health Science, University of Peloponnese, Tripolis, Greece
[c]Department of Obstetrics and Gynaecology, National and Kapodistrian University of Athens, Atina, Greece

ABSTRACT Streptococcal infection remains the leading cause of neonatal sepsis and death. Systematic use of antibiotic prophylaxis and advanced neonatal care guidelines aiming in the restriction and elimination of adverse effects on neonatal *Group B Streptococcus* disease neither eliminated it nor restricted it. Maternal immunisation with a *Group B Streptococcus* vaccine is considered the best strategy for the prevention of both early and late-onset invasive *Group B Streptococcus* disease. However, such an effective vaccine has yet to be fully licensed, although various attempts through the years have been made. At present, a hexavalent Ia, Ib, II, III, IV and V glyco-conjugate vaccine has completed Phase I clinical trials, showed promising results among healthy adults and was allowed to undergo Phase II trials. The early observations are promising allowing larger studies for determining the factors of optimal efficacy, such as timing of administration. The specific timing of administering a *Group B Streptococcus* vaccine during pregnancy has yet to be determined, although evidence show that for maximum levels of anti *Group B Streptococcus* antibodies to be transferred to the fetus, the best time of administration is during the second half of pregnancy or early on the third trimester. Furthermore, it remains uncertain if the vaccine should be recommended to all pregnant women, only those at higher risk or those testing positive, nor are specified the benefits of a second dose. In addition, a large Phase III clinical trial is required in order to evaluate possible adverse effects, including neuro-developmental assessments of the infants born to vaccinated mothers prior to licensing any vaccine candidate.

Keywords: *Group B Streptococcus; Group B Streptococcus* vaccine; *Group B Streptococcus* pregnant women; *Group B Streptococcus* neonates

Women of reproductive age should be immunised at childhood against poliomyelitis, measles, mumps, rubella, varicella, tetanus and diphtheria or to have natural protection after clinical or sub-clinical infection with all or some of the above pathogens. However, the level of childhood immunity through vaccination decreases through the years, resulting at childbearing age in relatively low levels of maternal antibodies insufficient to protect the infant.[1] Thus, vaccination is recommended during pregnancy against specific pathogens to develop protective immunity for the mother and her infant.[2] Such a routinely recommended vaccine during each pregnancy is seasonal influenza vaccine. Furthermore, depending on the emerging risk at pregnancy, other childhood vaccines may be recommended by the World Health Organization (WHO), such as the targeted vaccination for *tetanus-diftheritida*.[3]

Ideally, all women at childbearing age should be immunised against infectious diseases affecting conception, due to the fact that some of the pregnancies are unplanned. Pregnant women should be evaluated prenatally by their physician or midwife for their immunisation status, thus, the administration of the appropriate vaccinations.[4] The strategy is, to boost existing levels of circulating antibodies in hope that sufficient numbers will cross the placenta and protect the foetus from the second trimester of gestation and

Correspondence: Akylas GRAMMENIATIS
Department of Obstetrics and Gynaecology, Royal Free Hospital NHS Foundation Trust, London, United Kingdom
E-mail: akylas.grammeniatis@nhs.net

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on.[5] In this manner, infants could be protected against common viruses as well as various infections during their first weeks after birth when adequate quantities of immunoglobulin G (IgG) maternal antibodies will have been passed from the mother to her foetus, able to protect the newly borns for the time their immune systems grow.[6] After the first evaluation of the immune status of the pregnant, vaccinations can be administered by nurses, midwives or physicians who are in the ideal position to pass useful information to a pregnant woman.[2] Thus, they should be thoroughly informed on the subject to properly approach the pregnant woman helping her overcome any fear and hesitation in being immunised.[7] Although knowledge that there is no known harm to the woman or her foetus from inactivated vaccinations administered during the early third trimester is well established, concerns regarding safety have been raised among pregnant women for these and other types of vaccines.[8]

RECOMMENDED VACCINES IN PREGNANCY

The evidence accumulated have shown that there is not a risk to vaccinated pregnant women with inactivated vaccines for viruses and bacteria or toxoids, including *tetanus-diftheritida* and influenza.[9] Therefore, WHO, after evaluation of risk vs. benefit, recommends as a routine the vaccination of pregnant women with tetanus and diphtheria vaccine, the inactivated trivalent influenza vaccine, and recently, the formulation of *acellular pertussis* vaccine in combination with *tetanus* and *diphtheria toxoids*.[3,10] Hepatitis A and B vaccines, *meningococcal type A* and pneumococcal vaccines, polio and even yellow fever vaccines are recommended as well in certain high risk areas or endemic regions for pregnant women.[3] On the other hand, we should keep in mind that every woman after delivery can have any specific vaccine needed with no risk for her newly born.[11] Safety for the above is well established and pregnant women are most likely positively thinking of vaccination, but this may not be the case with newer and not widely used or known vaccines, or for vaccines that the benefits of protection may not be evident to the general public. One such vaccine, that is under development, is the one against *Group B Streptococcus* (GBS).

GBS AND THE OUTCOME OF INFECTION DURING PREGNANCY

GBS, main pathogenic species *Streptococcus agalactiae,* colonises the gastrointestinal and genitourinary tract to more than 50% of healthy adults.[12] A proportion around 11-35% of women can have GBS bacteria in their gastrointestinal or genital tract resulting, without prophylaxis, in about 1% of invasive neonatal GBS infection.[13] GBS is the commonest cause of sepsis and meningitis in infants up to the age of 3 months of age, followed by a significant morbidity and mortality rate of 9.6-22% causing 90,000 stillbirths worldwide each year (1-4% of all GBS associated stillbirths) and approximately 3.5 million deliveries of preterm babies annually.[14,15] GBS is transmitted from mother-to-infant either during the peri-partum period or during the early time after birth. The mortality rate from severe GBS infection in neonates resulting in sepsis and meningitis was >50% in the 1970s.[16] During the 1990s, the Centers for Disease Control and Prevention published the first detailed guidelines for the prevention and treatment of neonatal GBS disease.[17] Since then, significant progress has been made following the implementation of antibiotics to all pregnant women who are GBS carriers and these guidelines have undergone several revisions due to accumulated knowledge as a result of the decline in early neonatal GBS disease incidence.[18,19] Pregnant women are now routinely screened for GBS carriage at 35-37 weeks of pregnancy, using vaginal and rectal samples for the isolation of the pathogen. Women testing positive to GBS, women who have delivered a severe GBS ill newborn in earlier pregnancy, as well as any other high-risk individuals, are routinely and preventively given prophylactic antibiotic treatment to minimise the possibility of vertical transmission during labour.[20] This strategy has resulted in the reduction of the early-onset invasive neonatal GBS disease incidence occurring from 0 to 6 days after birth with impressive decreases in mortality rates (Figure 1). Specifically, there was a significant decline in the early-onset neonatal GBS disease incidence from 1.7 cases per 1,000 neonates in 1990 to 0.34-0.37 per 1,000 in 2008, while death rates decreased from >50% in the 1970s to 15-25% in the 1980s and to less than 10% by the 1990s.[14,19]

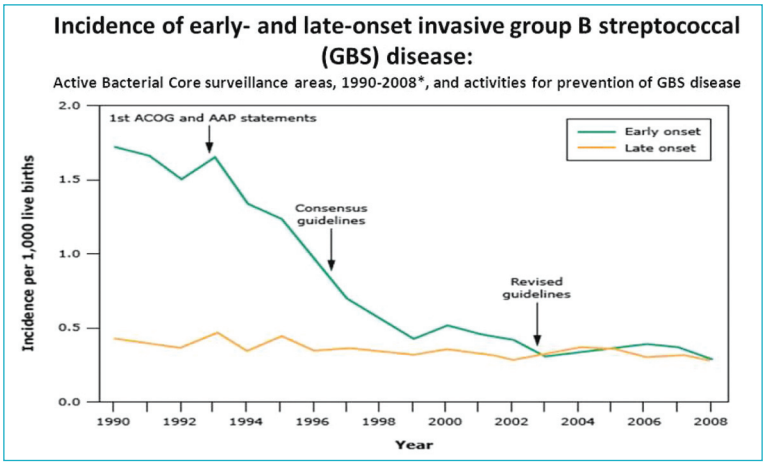

FIGURE 1: Incidence of early- and late-onset invasive group B streptococcal (GBS) disease. 1st -Reproduced from: Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(RR-10):1-36.
Original data form: Jordan HT, Farley MM, Craig A, Mohle-Boetani J, Harrison LH, Petit S, et al; Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network, CDC. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. Pediatr Infect Dis J. 2008;27(12):1057-64.

Unfortunately, intravenous benzylpenicillin is not that preventive for late-onset GBS neonatal infection that usually occurs 7 to 90 days from delivery.[21] Therefore, neither antibiotic prophylaxis nor the advanced neonatal care guidelines have eliminated neonatal GBS disease. They have improved incidence of morbidity and mortality, but GBS still remains the primary cause of sepsis and death in neonates, although steadily at ~0.34 to 0.49 cases of early and late-onset respectively per 1,000 live births.[22] Others report evidence of increasing rates (~4%) and significantly higher rates among premature neonates (10-30% vs. 2-3%).[20] Perhaps, the risk-based approach to prevention instead of obligatory screening leaves undetected cases, thus a significant proportion of colonised women unprotected. This could result in some nations to evidence of an alarming increase in cases compared to those adopting a screening policy.[21] The choice of screening programs comes with challenges, such as an increase of antibiotic usage and inevitably the risk of antibiotic resistance.[23] Decreased susceptibility to penicillin has been documented and other antibiotic choices are increasingly limited by concerns of resistance not only for GBS, but also other bacteria, such as *Escherichia coli* strains, causing neonatal infections.[16,24] About 30% of pregnant women receive antibiotics during labour potentially increasing the risk of resistant bacteria, including GBS, infecting the newborn, at an age that immune system immaturity does not allow immunisation.[25] Infants surviving streptococcal meningitis are left with long term neurological, thus mental defects increasing the importance of preventing maternal infection. Specifically, more than 20% of the infected newborns as a result of GBS meningitis will be severely affected long-term (cerebral palsy, learning difficulties, deafness, or global developmental delay), more than 5% will develop seizure episodes, whereas only less than two-thirds would be neurologically healthy.[26,27] These defects are important enough to justify the development of an effective and safe vaccine for pregnant women with the aim of eradicating neonatal sepsis and minimising child defects.[9]

It has been shown that premature neonates have only 29-51% of maternal antibodies compared to those of full-term.[28] Vaccination of mothers could pass higher antibody levels of protective antibody to their infants and protect them from late-onset disease regardless of birth time. Optimally targeting vaccination of mothers could in addition reduce screening costs and costs of antibiotic treatments, administered to about 30% of pregnant women.[25] The increase in prophylactic treatments increases the resistance of bacteria, not only putting at risk mother and infant,

but also spreading such strains at infant wards with significant consequences. It is well known that about 20% of clinical GBS isolates are resistant to clindamycin and 30-40% to erythromycin.[29] These resistant strains of GBS are a risk to immunosuppressed patients and the elderly as well, with significantly high case fatality rate reaching about 15%.[30]

Generally speaking, vaccination programs for other diseases at pregnancy are widely accepted because vaccines, such as for tetanus are highly effective as prevention methods in reducing morbidity and mortality among high-risk individuals. Glyco-conjugate vaccines against other capsulated bacteria, such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae type b*, have also proved highly effective.[31] Successes with the previous led to hopes for developing an effective vaccine against neonatal GBS disease. Such a vaccine, administered during pregnancy could be the best strategy not only for preventing early and late-onset invasive GBS disease, but also reducing the incidence of stillbirths and miscarriages.[14]

HISTORY OF GBS VACCINE DEVELOPMENT

POLYSACCHARIDE VACCINES

GBS has 2 distinct saccharides. One is group B carbohydrate that is common to all strains and the other, capsular polysaccharide (CPS) antigens conferring GBS serotype specificity. Ten different CPS antigens are recognised at present (Ia, Ib, II-IX). The protective role of antibodies against CPS Type III, thus considered a good candidate for an effective vaccine against GBS strains, was recognised as early as in the 1970's by Baker and Kasper.[32] GBS strains of Type III wasn't the dominant strain at that time being responsible for most of the neonatal infections caused by GBS. These early observations have resulted in the development of a vaccine against GBS serotype III showing under Phase II clinical trials good safety and acceptable immunogenicity.[33-36]

However, over the years, different serotypes such as Ia and V increased, thus increasing the need for developing a multivalent vaccine for protecting mothers and newborns against various serotypes.

Not all pregnant women develop sufficient levels of protective antibodies for their neonates. Interestingly, antibodies to Type III CPS were found in the cord blood of all healthy neonates from mothers having high antibody levels against GBS CPSs at the time of birth.[37] The mechanism of protection was attributed to placental transfer of high levels of protective IgG antibodies against CPS, providing passive immunity to infants. Thus, immunization of pregnant women against CPS should naturally prevent newborns from GBS infection.[38,39] However, these early attempts for developing a CPS based vaccine were abandoned after Phase I clinical trials, because they could not induce B-cell memory and activate T cells.[38]

GLYCO-CONJUGATE VACCINES

The abandonment of the idea of developing a polysaccharide vaccine turned interest to glyco-conjugated vaccines, due to success of a type b CPS-protein conjugate vaccine against *H. influenzae*.[40,41] Baker and Edwards back in 2003 observed that, although unconjugated polysaccharides are poorly immunogenic, their covalent coupling with protein stimulates T cell dependent antigenic recognition profoundly enhancing immunogenicity.[37] Similarly, a CPS-protein vaccine using a GBS III CPS-tetanus toxoid (III-TT) glyco-conjugate preparation was successfully used in the immunization of people.[42] These evidence confirmed that covalent conjugation of a protein and a CPS induces B-cell memory against the polysaccharide. B-cell receptors bind to the carbohydrate portion of the glyco-conjugate vaccine, signaling B and T cell activation causing B cell proliferation and also differentiation. B and T- cell memory induction result subsequently in a robust IgG response through antibody class switching.[43]

In the case of GBS infection, increasing CPS-specific IgG in the cervico-vaginal fluid, is important because, if vaginal and rectal GBS carriage is decreased, in addition to passively immunising the infant, the risk of infant infection during delivery should also be decreased. Indeed, a recent trial found that women immunised with a GBS CPS III-TT conjugate vaccine had decreased levels of vaginal and rectal colonisation with GBS, the source of neonatal GBS sepsis and meningitis.[44] This multicenter, ran-

domised trial showed an efficacy of 36% in delaying the time to first acquisition of vaginal Type III GBS colonisation and 43% in rectal colonisation through III CPS-specific IgG transfer from serum into vaginal and rectal fluid.[45] Protective IgG antibody titres to Type III CPS were elevated in cord blood and persisted for at least 2 months after birth, highly correlating in levels with those of Type III CPS-specific antibody in maternal serum.[37] These polysaccharide conjugate vaccines (PCV) appeared safer and more effective compared to polysaccharide-only vaccines, indicating that we can prevent neonatal GBS infection through maternal vaccination. However, prevention of Type III GBS strains colonization exposed women to colonisation from other GBS serotypes, such as Ia, Ib, II, III, and V, that was estimated to account for approximately 97% of invasive isolates in the areas examined worldwide.[46] These observations initiated the development of a novel hexavalent CPS conjugate vaccine covering the majority of invasive GBS serotypes. The preparations including Ia, Ib, II, III, IV and V serotypes was found to be sufficiently immunogenic, protecting from GBS infection.[47] Thus, it was put in clinical trials in hope of preventing perinatal exposure, but also reduce genital tract and rectal colonisation.[48] Pharmaceutical companies have already developed different versions of multivalent vaccines choosing as antigens the most prevalent serotypes. A trivalent conjugate vaccine using the mutant diphtheria toxin, cross reactive material 197 (CRM197) and the polysaccharides of serotypes Ia, Ib and III, responsible for 78.8% of invasive GBS neonatal disease worldwide proved after Phase Ib/II clinical trial (NCT01193920) that infants born from women receiving it had higher CPS-specific antibody levels at birth than after 43 and 91 days post-partum.[49,50] Another attempt included a pentavalent preparation of GBS PCV targeting Ia, Ib, II, III and V serotypes (NCT03170609) and a third attempt combined a PCV Type III CPS and beta C protein producing protective levels of antibodies against both components.[36] Despite the promising results of the above clinical trials, the risk of immune interference if similar type of conjugate vaccines is given as well as serotype redistribution worldwide and potential switching, redirected efforts for GBS vaccine development; researchers' aim was to discover unique antigens that could induce a strong immune response against the majority of the GBS strains.[51-53] Using these structurally conserved protein antigens to create a broad coverage GBS protein-based vaccine appeared very attractive as well as cost-effective among different vaccine candidates (Table 1).[54]

APPLICATION OF REVERSE VACCINOLOGY TO GBS VACCINE DEVELOPMENT

Reverse vaccinology, first used by Rappuoli in 2000, describes a method for vaccine design using the information obtained from whole-genome analysis of a pathogen.[55] Reverse vaccinology was firstly used against *N. meningitidis* (*meningococcus*), a gram-negative coccus that is the second most common cause of bacterial meningitis in adults and 11- to 17-year-old children.[56] Using bioinformatics, one identifies protein antigens that may be immunogenic, thus potential vaccine targets. Antigens identified by se-

TABLE 1: Summary of different vaccine candidates.

Summary of different vaccine candidates					
Vaccine candidate	**Preclinical**	**Phase I**	**Phase II**	**Trials in pregnant women**	**Phase III**
Monovalent and bivalent conjugates tetanus toxid/CRM197-CPS)	x	x	x	x	
Trivalent CMR197- CPS concugates	x	x	x	x	
Hexavalent CRM197- CPS concugates	x	x	x	x	
N-terminal domains of the Rib and AlphaC proteins	x	x			
Pilus proteins	x				
Other proteins	x				
Biotinylalted CPS concugates	x				

CRM 197: Cross reactive material 197; CPS: Capsular polysaccharide.

quencing the genome and pinpointing the open reading frames (i.e., potential DNA coding regions) that encode for surface-exposed proteins have specific characteristics, such as homology to known membrane proteins.[57] Purified antigens are eventually injected to mice or other animals and the in vitro killing of bacteria by their sera is explored.[58] Theoretically, this new concept of vaccine development overcomes the problems of conventional vaccinology, such as antigen quantity, requiring isolation of the targeted pathogen. Reverse vaccinology depends only on the over-expression of these antigens in other organisms, allowing vaccines to be developed against pathogens that are difficult to isolate by culturing.[58] Vaccine development for GBS has used similar approaches. 589 surface antigens were selected from the genomic sequences of eight clinical GBS strains, 312 of which could be reproduced in E. coli and purified for use.[59] Thus the key difference between reverse and conventional vaccinology is that the first uses unknown antigens discovered through molecular screening of multiple strains for potential antigens while the second, well-characterised antigens with a known role in pathogenesis. However, this approach did not identify CPS used in previous attempts, as a potential vaccine candidate. This finding illustrates the inability of reverse vaccinology to discover antigens that are not directly encoded by the genome.

Despite the fact that several vaccine candidates against bacterial CPSs have been developed by now in addition to the trivalent or the hexavalent which are currently being tested in pregnant women, surprisingly little is known about the mechanisms involved in the development of protective immunity against a CPS; in the traditional model for glyco-conjugate vaccines, B-cell receptors specific to a vaccine's carbohydrate components recognise and phagocytose the glyco-conjugate.[38,44,60,61] After phagocytosis, the glyco-conjugate is destroyed in B-cell endosomes, and the peptide, but not the carbohydrate components, are expressed on major histocompatibility complex (MHC) II molecules.[51] The MHC II-peptide complexes activate T-cell receptors, causing T cells to create interleukin (IL) 2 and IL-2 receptors, stimulating other T cells to produce IL-4, triggering B-cell maturation, class switching, and memory development. As a result, the B-cell is primed to continuously produce antibodies targeting the carbohydrate components of the glyco-conjugates, while T cells target peptide components.[43] These carbohydrate components are digested in the endosome and can only be separated from the cell surface on MHC II molecules when they are covalently bound to peptides. On the other hand, conventional vaccines are based on polysaccharide chains having few covalent connections to proteins per polysaccharide; thus, having a relatively small number of glycano-peptides.[38] To overcome the drawbacks and increase effectiveness, the authors conjugated polysaccharide with peptides, rather than proteins, obtaining maximum number of glycan-MHC II-binding peptide linkages per glyco-conjugate. This new-generation vaccines were significantly improving the survival of challenged mouse pups because they were in a mouse experimental model, 50-100 times more immunogenic than a standard glyco-conjugate vaccine.[43] The experiments showed a potentially better protection of such type of a vaccine for late-onset GBS infection that typically occurs in neonates born prematurely and having decreased levels of trans-placentally transferred antibodies.[62] A potential answer to the problem of early as well as late-onset GBS illness, however, could be maternal immunisation.

SUMMARY OF CURRENT KNOWLEDGE ON GBS VACCINES

In summary, prophylactic risk-based treatments to protect pregnant women have improved the prevelance of fetal loss, stillbirth, premature births, low birth weight, infection after birth and deadly clinical disease. Healthier mothers and newborns require fewer medical treatments, such as antibiotics, and other costs of care throughout pregnancy and after birth. Researchers estimate that in order for a GBS vaccine candidate to be more likely to be licensed for pregnant women should have >80% efficacy as well as 90% or even higher global coverage, in order to prevent thousands of stillbirths and infant deaths annually. The evidence are also promising for the effects of immunisation, but we should really focus on the prevalence of GBS infections and strains involved in different geographic regions as well as socioeco-

nomic situations must first be determined to fully address effectiveness.[63] GBS colonisation, GBS serotype redistribution worldwide as well as GBS associated morbidity and mortality rates among neonates and involved serotype prevelance for unveiling invasive isolates would play a key role in GBS vaccine development.[64] Multiplex polymerase chain reaction could be a reliable method for evaluating the impact of immunisation for the ongoing vaccine development against GBS.[35,36] Reliable epidemiological information on the vaccine effectiveness and safety will help women and their health care providers to overcome their concerns. Such concerns are also related to culture, traditions and religious or political socioeconomic status, and must be taken into consideration, but they are not only them. Many other practical factors should be considered when calculating cost effectiveness apart from the cost itself, such as the form of vaccine distribution (vials of one or multiple doses), the product stability under various environmental conditions, the time of administration and the frequency of vaccination.[65] Educating and providing detailed information about the risks and health benefits of GBS neonatal disease and maternal vaccination respectively, could make the difference in helping pregnant women to decide whether to be vaccinated or not. Optimally, the vaccine should be administered early in the third trimester of pregnancy to include as many as possible of the 30% of GBS cases of premature births.[18] Thus, more knowledge about GBS infection outcomes is needed for convincing pregnant women to accept such a vaccine as part of their prenatal care.[66-68]

Additionally, the production of an effective and safe vaccine depends on good knowledge of the immune mechanisms involved. Stimulation of T-cells, could be important in antibody production among women previously colonised with GBS compared to GBS naïve women and the possible boosting effect on previously exposed or immunised individuals must be explored. Areas of immune response exploration are the path of GBS antibody activities, such as avidity, affinity, opsono-phagocytic killing, antibody subtype and isotype distribution, vaginal antibody presence and its influence on vaginal GBS colonisation. Knowledge of antibody production and potential transfer through breastfeeding, length of protection conferred the first months of a neonate's life and the possibility of protection in future pregnancies, would be really important as well. Apart from being highly effective on early and late-onset GBS illness, the vaccine should be able to easily fit in the current targeted immunisation programs of different nations across the globe.[69] Thus, it should avoid interference with other vaccines' immune response that are given simultaneously in prenatal care programs, such as TT vaccines.[70] Aiming in wide distribution, it should be affordable and should meet common technical limitations, such as refrigeration and storage.[71] As to optimal timing of vaccination, the best time could be during the second or third trimester of pregnancy ensuring long-term GBS immunity. Most neonatal GBS illness occurs in the first few hours of life and timing of vaccination must result in passive transfer of protective antibodies from mother to neonate. Recent studies in non-pregnant women aiming in evaluating how many doses should be administered for optimal immunity revealed that when the second dose was given 4-6 years after the administration of the 1st dose of a trivalent (Ia, Ib and III) CRM 197 conjugate vaccine, there was a >200-fold rise of the maternal antibodies circulating. On the other hand, no increase was shown when the second dose was given 1 month after the first administration, suggesting that further doses might be required in subsequent pregnancies. Various formulations of GBS vaccine candidates are being tested in present clinical trials, but none has been approved at the time of writing, since several obstacles exist in moving the most promising vaccines into larger Phase III clinical trials. In view of the low incidence of GBS infection rates in Europe and United States of America, vaccine efficacy can only be determined with large numbers of participants, making the evaluation of the vaccines even more difficult. GBS can undergo capsular-type switching through horizontal transfer of the capsular locus as has been already proved, being a known limitation of the use of polysaccharide-protein conjugate vaccine. Finally, new studies focus on efforts to identify common proteins to all GBS strains in order to better define vac-

cine targets and develop a vaccine that would offer protection against all GBS serotypes.

CONCLUSION

An antenatal administration of a GBS vaccine, administered possibly to all pregnant women through prenatal health programs could protect against prenatal, early and late-onset illness, reducing both the risk of antibiotic-resistant infections and the incidence of GBS disease in infants. Currently, a hexavalent GBS vaccine has successfully undergone Phase I/II clinical trials (NCT03765073) to evaluate the safety, tolerance and immunogenicity and is now evaluated among pregnant women in Phase III. The preliminary evidence show that it will soon be added to the list of vaccines now available to protect mothers and their newborns against important and often fatal infections, such as tetanus, influenza, pertussis, and meningococcal meningitis. Glyco-conjugate vaccines have a proven track record of effectiveness, but the recent advances of reverse vaccinology and the clarification of the mechanism of glyco-conjugate vaccine-induced immunity has helped the development of a new generation of immunogenic vaccines, including multivalent GBS bacterial CPS-CRM 197 conjugate vaccines, CPS protein conjugate vaccines and multivalent adjuvanted protein vaccines (NCT03807245). Protein vaccines are in earlier stages of development, but are highly promising as they might confer protection irrespectively of serotype. GBS serotype specific polysaccharide-protein conjugate vaccines are at advanced stages of development, but a large number of participants would be required to undertake Phase III clinical trials, followed by Phase IV studies to evaluate safety and efficacy. If these vaccinations prove successful introducing them in regular prenatal care, will perhaps result in the improvement of global public health by lowering maternal and newborn morbidity and mortality due to GBS infection of women at child barring age.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Akylas Grammeniatis;* ***Design:*** *Akylas Grammeniatis;* ***Control/Supervision:*** *Angeliki Rothi Burriel, Kalliopi Pappa;* ***Data Collection and/or Processing:*** *Akylas Grammeniatis;* ***Analysis and/or Interpretation:*** *Akylas Grammeniatis;* ***Literature Review:*** *Akylas Grammeniatis;* ***Writing the Article:*** *Akylas Grammeniatis;* ***Critical Review:*** *Angeliki Rothi Burriel, Anastasios Ioannidis.*

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