A credible GBS vaccine – finally back on the agenda

LONDON, UK----20th June 2010----ExpertREACT. Group B *Streptococcus* (GBS) still places considerable burden on maternal and neonatal health despite the widespread implementation of screening and intrapartum antibiotic prophylaxis (IAP). Historic pioneering work with GBS vaccines, although frustrated with safety concerns, still guides Novartis Vaccines to pursue this much needed intervention. **VacZine Analytics** discusses the issues.

Recently the UK Health Protection Agency (HPA), Centre of Infections, London held a symposium regarding advances in the diagnosis, management and treatment of neonatal group B *streptococcal* (GBS) infections. Attendees from numerous disciplines including public health (US ACIP), neonatology, midwifery, pediatrics, microbiology and vaccinology came together to discuss the current understanding of the challenges posed by the pathogen but more importantly, what near and long-term intervention(s) might further reduce disease burden. **VacZine Analytics** was in attendance at the symposium and summarizes the key issues with an emphasis on the prospects for a preventative GBS vaccine.

Group B Streptococcus (GBS) or *S.agalactiae* was first reported as a human pathogen in 1938 as a cause of fatal puerperal sepsis **(1).** Awareness of its importance and potential lethality later escalated with the publication in 1969 of a cluster of 9 neonatal infections in Boston published in the New England Journal of Medicine (NEJM) **(2).** Indeed, once monitored GBS became the leading cause of septicemia and meningitis in neonates and infants < 3 months throughout the 1970s.

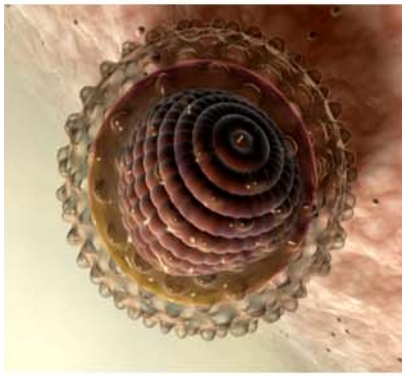
GBS is vertically transmitted from the vagina of a colonized pregnant woman (10-30% prevalence) during childbirth where approximately 50% of neonates are colonized. In around 2% of colonized newborns, consequent GBS infections can then manifest themselves as either early-onset (EOD) within 0-6 days (90% in first 24hrs) or late-onset (LOD, 7-89 days). Early onset infections can either be bacteremia (or septicemia), pneumonia and meningitis, with predominance on bacteremia. Late onset infections are distinct with a median delay of 36 days, bacteremia without focus and meningitis are common. Historically the incidence of early onset infection in neonates ranged from 1 to 3 per 1000 live births, which in the 1970s equated to 8-10,000 cases per year **(3).** Significantly, around 25-50% of survivors of GBS meningitis (either EOD or LOD) have permanent neurologic sequelae. The incidence of LOD is around 0.5 per 1000 live births.

In an effort to reduce the morbidity and mortality associated with neonatal GBS infection, US health authorities and relevant stakeholders (CDC, ACOG, AAP) have implemented successive recommendations/guidelines in both 1996 **(4)** and 2002 **(5).** In 1996, the first set of guidelines advocated the use of either risk-based or culture based screening to identify women that should be offered intrapartum antibiotic chemoprophylaxis (IAP) to prevent GBS infection. Example risk factors were: delivery at <37 weeks gestation, and elevated intrapartum temperature > 38^{o}C. The culture based screening approach involved treating all pregnant women who were GBS colonized at 35-37 weeks (IAP). Although implementation of these guidelines had a noticeable impact on the incidence of EOD, the same authorities came together to formulate a 2002 revision which essentially reinforced the universal screening based approach to all women at 35-37 weeks so eliminating the potential risk of "missing" cases *via* the risk-based approach.

In retrospect, universal screening policies to prevent neonatal GBS have been successful. Since the implementation of the first US prevention efforts from 1996, the incidence of EOD declined by 70% to 0.5 cases per 1000 live births in 1999. An up to date review published by Phares CJ et al in 2008, suggested that the incidence of EOD decreased further from 0.47/1000 births in 1999-2001 to 0.34/1000 live births in 2003-2005; a relative reduction of 27% **(6).** Significantly, the incidence of LOD has remained relatively constant during the era of IAP with around ~1000 US cases per year. According to GBS experts a credible explanation for why GBS LOD remains constant is currently lacking although interesting hypotheses such as intra-familial transmission of the pathogen in the household were put forward at the symposium.

Many other countries have also implemented similar universal screening guidelines to the US, with notable successful case studies presented at the HPA symposium from Germany and Spain. In Spain, which also revised its guidelines in 2003, data was presented from the Castrillo network of 34 hospitals accounting for 25% of Spanish births (~105,000) **(7).** Despite comments regarding isolated cases of poor implementation of IAP, again the incidence of EOD in Spain has been reduced to 0.31/1000 births in 2009 but LOD has remained unaffected.

The United Kingdom is a noticeable exception in that authorities do not currently advocate universal GBS screening. A number of reasons for this seemingly resistant policy stance were discussed at the symposium. Issues such as cost, fear of widespread antibiotic resistance generation, antibiotic hypersensitivity were raised. Many were dismissed by experts as valid reasons to not screen due to lack of compelling supporting evidence from countries that are operating GBS screening programs. Representatives from UK Charities such as Group B Strep Support (GBSS) presented the perspective of the parent of why the UK should screen for GBS.



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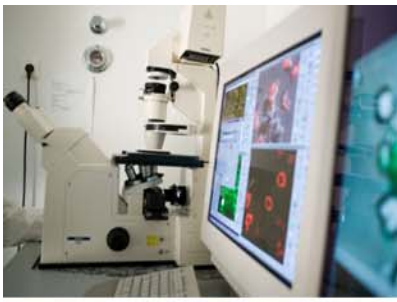
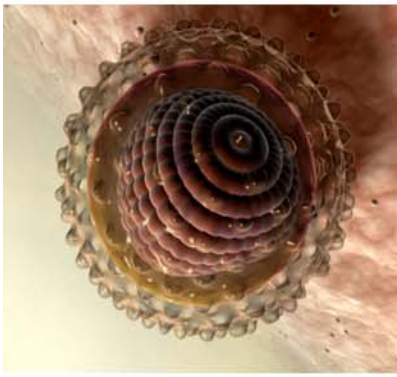
An intriguing topic at the recent symposium was the discussion of a GBS preventative vaccine. Although research within the field has been ongoing for decades, the availability of vaccine for widespread use is still a number of years away. Unfortunately commercial GBS vaccine development has been frustrated (unnecessarily) by safety concerns in the US due to the connection with pregnancy.

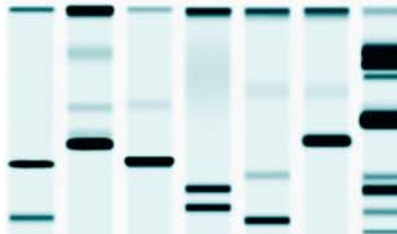
A GBS vaccine is still an attractive proposition because pioneering work in the 1970s established the presence of GBS anti-capsular polysaccharide IgG as a potential correlate of immunity to GBS serotype III, a dominant form in both EOD and LOD **(8 and others).** Conceptually, this antibody (which is protective at 10ug/ml, ~91% risk reduction) could be raised within the female of childbearing age and protect the neonate by transplacental transfer during the third trimester of pregnancy. Regarding the deployment of such a vaccine, there are still many issues open for debate (as observed at the symposium). For example, who would the vaccine best be given to? Like human papilloma virus (HPV) and *meningococcal* vaccines, a GBS vaccine could be given to the adolescent population, or would it be more suited to older women closer to childbearing? It is also interesting to consider what role a vaccine would play alongside screening + IAP and whether it could impact upon maternal GBS and LOD GBS disease. A GBS vaccine almost certainly would not be developed for pregnant women.

Novartis Vaccines are developing a CRM-glycoconjugate GBS vaccine containing serotypes 1a, 1b, III and V which theoretically should cover 85% of GBS strains. The company started a Phase I study in December 2007 in healthy non-pregnant women 18-40 yrs (NCT00657683, Swiss Medic) which has been completed although results have not been released into the public domain. Another Phase I study (NCT01150123, Belgium) has started May 2010 again in the same target population but with trial arms investigating different dose levels, adjuvants and numbers of injections. The company is working with a consortium known as DEVANI (A 7th Framework Program) which also presented data at the symposium **(9)** and continues to discuss its work regarding GBS pilus proteins as potential vaccine candidates, although these are still at the pre-clinical stages **(10)**

It would appear Novartis Vaccines are taking a GBS vaccine seriously, and are ahead of competitors. With a large potential market forecasted by **VacZine Analytics (11),** strong advocacy from powerful stakeholders and most of all, a vaccine mechanism of action with high probability of success – this is a good decision, especially for future expectant mothers.







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References and Notes:

Abbreviations: American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP)

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