Rethinking new meningitis ACWY vaccines

LONDON, UK----17th November 2009----ExpertREACT. At the recent Meningitis Research Foundation (MRF) meeting in London (12th & 13th November 2009), new vaccines to protect against *N.meningitidis* (ACWY) were discussed. Question marks around inclusion on the US infant schedule will force manufacturers to consider other penetration strategies. **VacZine Analytics** discusses the current issues.

Alongside other important pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* Gram-negative *Neisseria meningitidis (N.men)* is an important contributor to bacterial meningitis. Of the estimated 1.2 million cases which occur each year (WHO Figures), N.men is thought to be responsible for around 40% of the total where 5 main serogroups ACWY and B are responsible for the majority of disease. These serogroups notably exhibit different distribution patterns around the world with serogroups B, C and Y being the most common in Western countries and serogroup A, highly prevalent in the "meningitis belt" of sub-Saharan Africa. In all instances, *meningococcal* disease, which is often difficult to detect early, causes substantial morbidity and mortality, especially in infants.

In Western countries, the incidence of meningococcal disease ranges from 0.34 (US) to 1.1 (Europe) cases per 100,000 inhabitants, although within Europe the rate can vary widely e.g. Ireland >4 cases per 100,000 inhabitants **(1).** The number of cases in these regions has been declining over the past decade due to the implementation of serogroup C conjugate vaccination but also due to a "trough" in a long-term cycle, as 10-15 year cyclical variations in meningococcal disease incidence occur. As well as noticeable trends in incidence, other important dynamics are changes in serogroup distribution such as the recent predominance of serogroup Y in the United States.

Vaccines to prevent meningococcal disease are considered an effective public health strategy, with undoubtedly the most successful case study, being the implementation of group C vaccination, first initiated in the UK. The group C vaccine was introduced in 1999 for all young children and individuals to the age of 19 years (catch-up campaign). Infants received a 3 dose priming series (without booster) which was later switched due to observed antibody waning in 2006 to a 2 dose series (3 and 4 mos) with boosting at 12 mos. Prior to vaccine implementation of the vaccine, around 150 deaths (40 among adolescents) occurred due to serogroup C. This figure has been reduced to virtually zero in the space of 10 years because of high vaccine coverage and effectiveness rates of >85% **(2).**

At the MRF meeting, experts attributed the success of the UK MenC program to a combination of induction of herd immunity, direct protection against bactericidal antibody and the induction of immunological memory. The "herd effects" of the vaccine almost certainly reduced transmission from the adolescent population which previously exhibited high carriages rates of serogroup C. However, experts did note that additional strategies to prevent a remergence of group C disease should be considered since population levels of antibody and herd immunity are now waning.

Another notable vaccination strategy has been the introduction of quadrivalent conjugated ACWY (MCV4) vaccines in the US which were recommended for routine vaccination of pre-teens 11-12 yrs in 2005. The recommendation was revised to include all adolescents aged 11-18 yrs in June 2007 **(3)** and young children 2-10 yrs "at risk" due to underlying conditions. Unlike the UK menC program coverage levels have not been high, reaching about 30-40% **(4).** The incidence of meningococcal disease was at an historic low at MCV4 vaccination. Now it is unclear whether the program has had a great impact or will generate a "herd effect".

Bearing in mind US/EU meningitis vaccine policy and current disease epidemiology, commercial vaccine manufacturers are seeking ways to expand the market for meningitis vaccines. The main strategies include producing vaccines for infant use (<1 yrs) and extending coverage to serogroup B. For example, Novartis Vaccines recently filed Menveo, a new conjugated ACWY vaccine which, according to the company (at the MRF meeting) should receive approval for >11 yrs in the EU/USA in early 2010. Novartis will be challenging Sanofi Pasteur's Menactra (MCV4, 1 dose) which was recommended for adolescent vaccination by the US ACIP since 2005. Menactra recently reported a strong Q3 2009 with sales of €184m, a 19.7% increase on the same period last year **(5).** Both companies are aiming for an infant indication in the US.

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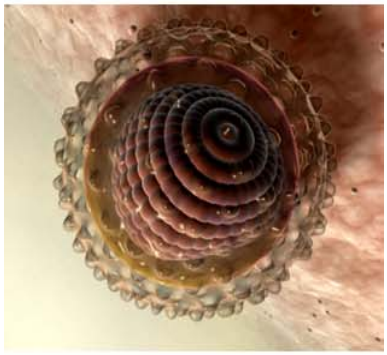

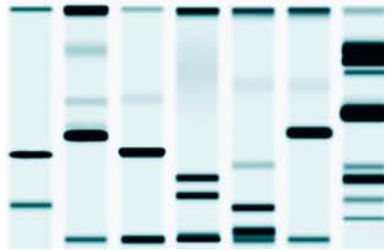

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GSK Biologicals, who are also developing a quadrivalent ACWY vaccine (Phase III), have a nearer term product MenHibrix, recently filed in the US**.** MenHibrix, containing antigens to Hib and N.men serogroups C & Y, is a three dose series (2,4, 6 mos) with a boost at 12-15 mos. The vaccine is designed to compliment other "non Hib" GSK vaccine products in the US infant series such as Pediarix and Rotarix. The vaccine would minimise the additional injections that would be required with Menactra (1+1 doses) and Menveo (3+1 doses).

At the MRF meeting a representative of the US CDC pointed out relevant issues regarding potential ACIP recommendation of new meningitis ACWY vaccines in US infants **(6).** This is an important topic because the majority of US disease occurs in the <1 yrs group **(7)** and, manufacturers are pushing hard for recommendation of newer vaccines. Although on average there have been 15 annual US deaths due to meningococcal disease in the <1 yr group (1999-2008), the current potential of vaccine preventable disease in infants is considered low when compared to adolescents. Indeed, the majority of disease is caused by serogroup B (US ABC data). Also it is clear that "programmatic considerations" have been high on the agenda. For example, GSK's MenHibrix, although not adding additional shots would potentially skew use away from Hib containing pediatric combinations. For Menveo and Menactra, both would require additional shots with Menactra (starting at 9 mos) missing the 6-12 month age group at risk. Other potential issues involve vaccine interchangability, opportunity costs, decisions on catch-up recommendations and an uncertain need for boosting.

The "lukewarm" US experience of MenACWY vaccination in teenagers has left many unanswered questions which are undoubtedly impacting upon discussions focused on infants. Based on the UK experience, it is possible that driving higher coverage in US adolescents may provide indirect protection in infants with less public health "costs" than infant vaccination. With UK experts also suggesting re-boosting of adolescents due to waning immunity and a recent re-vaccination (every 5 yrs) recommendation from ACIP **(8)** it is highly likely manufacturers will turn their attention back to promoting use in older groups e.g. college entrants, "at risk", Haj travellers. This of course means a market share battle for Novartis in the US against incumbent Sanofi Pasteur and is not the immediate blockbuster the Swiss company hoped for. Now it seems it is all eyes to *meningococcus* serogroup B vaccines.

References and Notes:

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