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New vaccines for *Staphylococcus aureus*: risk-based or population-based approach?

LONDON, UK----12 April 2008----ExpertREACT. New research (1) conducted by **VacZine Analytics(R)** focused on methicillin-resistant *Staphylococcus aureus* (MRSA) highlights continued expert concerns regarding the transmission of the pathogen in the community (CA-MRSA) as well as hospital settings. For vaccine manufacturers the research raises the question of whether new vaccines should cover antigens specific to CA-MRSA and whether they should be positioned as part of a wider population-based approach beyond "at risk" groups.

Staphylococcus aureus or "Staph" is a ubiquitous gram-positive spore forming bacterium which colonizes around 20-30% of normal healthy humans on the skin and mucosal surfaces such as the nose and perineum. Ordinarily the bacterium is harmless but in certain cases when it enters the body it can cause serious disease. Staph is a major cause of skin and soft tissue infections (SSTIs), bone infections, endocarditis and bacteremia (blood poisoning, sepsis) all of which can have fatal outcomes.

Many in the "lay" population are familiar with the drug resistant form of *Staph* known as **MRSA** which stands for methicillin-resistant *Staphylococcus aureus.* MRSA was first identified in the early 1960s and has presented great challenges to physicians especially in intensive care units (ICUs) of hospitals. In ICUs patients are critically ill often recovering from trauma (burns) and deeply invasive procedures for example, after cardiothoracic surgery, orthopaedic surgery and transplant procedures. Because ICU patients are commonly elderly and/or immunocompromised they are susceptible to post-operative wound/surgical site infections, bacteremia and pneumonia. In some cases these infections are initiated by a self-colonizing strain of Staph. If the resultant infection is caused by MRSA (around 50% of cases), it is associated with greater length of hospital stay, higher mortality and greater costs. In 2005, the US Centers for Disease Control and Prevention (CDC) estimated that around 94,000 people had an invasive MRSA infection of which 18,650 died in a hospital setting (2).

Although there are a number of drugs such as vancomycin, linezolid and daptomycin approved for the treatment of serious hospital-acquired MRSA infections, many experts agree that evolving bacterial resistance will remain a continuous threat. Experts therefore strongly advocate the use of complimentary risk-avoidance strategies. For example, it is documented that one of the main sources of cross-transmission of Staph is *via* the hands of healthcare workers, a source that can be prevented by strict hygiene measures. Other evolving strategies involve the "swabbing" of patients due to be hospitalized to check for MRSA colonization so as to guide downstream management. In some countries such as Holland and those in the Nordic region, these techniques of patient isolation along with strict antibiotic prescribing policies have resulted in very low rates of MRSA when compared to countries such as the US and UK.

In recent years the threat of MRSA has also become apparent outside of the hospital setting with the recently described phenomenon of community-acquired MRSA (CA-MRSA). For example, in the US, outbreaks of CA-MRSA have occurred in diverse populations such as American Indian, Alaskan Natives, sportsmen, prisoners and healthy children. CA-MRSA mostly causes treatable skin and soft tissue infections but in some cases (5-7%) isolates can be invasive and responsible for severe necrotizing disease e.g. pneumonia which follows a rapid, often fatal course. A 2007 study published in JAMA estimated that of 8967 observed cases of invasive MRSA in the United States, around 13-14% were community-associated (3)

Invasive CA-MRSA isolates are epidemiologically distinct from strains transmitted in the hospital (HA-MRSA). Although they tend to be resistant to fewer classes of antibiotics, they are "fitter", more virulent and produce toxins including the notable Panton Valentine Leukocidin (PVL) necrotic cytotoxin (PVL) observed in the epidemic strain USA300. When interviewed, experts were most concerned that PVL+ CA-MRSA could cause rapid disease in individuals with no discernible risk factors or recent contact with healthcare facilities. More importantly, they felt incidence was rising and that more could be done to equip primary care physicians to recognize and treat early CA-MRSA skin infections which were often confused with "spider bites".

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Because of these concerns and urgency to update wider understanding of CA-MRSA, healthcare policy makers are now focusing on educating primary care physicians. A good example is in the UK where a new set of treatment guidelines for dealing with CA-MRSA infections are soon to be published (4).

As well as drug treatments and risk-avoidance strategies, interviewed experts believed that the development of a Staph preventative vaccine was also worthwhile pursuit. Such a vaccine could prevent the incidence of Staph bacteremias, wound infections or in the ideal scenario, nasal carriage possibly after decolonization with the antibiotic murpirocin. Despite the high profile of US-based NABI's Type 5/8 polysaccharide conjugated vaccine in 2005 (Phase III), it is clear that the field is again resurgent with Merck & Co currently testing a single antigen vaccine (Phase II) in end-stage renal disease (ESRD) and cardiothoracic patients scheduled for surgery. Merck & Co acquired the vaccine antigen from Vienna based Intercell AG in an exclusive arrangement prior to its strategic alliance with Novartis Vaccines. Presently it is the most advanced program with expected filing in 2012-2014.

Aside from the effort at Merck & Co's many believe that in order for a Staph vaccine to be effective it should contain a mixture of antigens, some specific to CA-MRSA isolates. NABI are seemingly capitalizing on this latter concept by relaunching a pentavalent StaphVAX effort which contains additional antigens such as PVL, Type 336 and alpha toxin. In addition, a recent analysis of vaccine preclinical intellectual property (5) indicates that other major companies such as GSK Biologicals and Novartis Vaccines are also pursuing Staph vaccine technologies.

According to the experts one key challenge for future Staph vaccines will be choosing the "right" antigens. Staph causes a wide spectrum of diseases and expresses many antigens during different growth conditions with numerous factors involved in pathogenesis, adherence and biofilm formation. While newer antigens such as Poly-N-acetyl glucosamine (PNAG), Fibronectin Binding Protein (FBP) and Staph heteropolymer have yielded some promising preclinical data many antigens are simply biological "red herrings".

A wider challenge beyond the technical aspects of Staph vaccine development is choosing an appropriate future vaccination strategy. Presently it does seem logical to protect defined groups at high risk from Staph bacteremias; however, many experts believe that in terms of overall societal burden, preventing Staph SSTIs and reducing carriage are also high priorities. Lessening these would involve some form of population-based vaccination with one expert venturing that a Staph vaccine should be on the paediatric schedule in the US. Opponents to this ambitious concept are likely to raise the issue of cost and the fear of "over vaccination" but at least in immunological terms the strategy makes sense. Potential vaccinees in the community would have more time to develop protective immunity than those merely vaccinated a few weeks before hospital entry.

References:

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About VacZine Analytics (R):
VacZine Analytics is an established research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.