Quadrivalent influenza vaccines – full switch or niche position?

LONDON, UK----12th June 2012----ExpertREACT. There is a strong rationale for adding an additional B strain to the current trivalent influenza vaccine. As a commercial lifecycle management initiative **VacZine Analytics** believes it is the most compelling so far. However, the temptation to premium price will most likely relegate QIVs to being another niche offering.

Seasonal influenza epidemics exert substantial morbidity and mortality in humans affecting approximately 5-15% of the population mainly with upper respiratory tract infections. On a global basis it is estimated by the WHO that influenza causes around 3-5 million cases of severe illness per year with an estimated 250,000 – 500,000 deaths. As much as 1 billion infections are thought to occur.

Influenza disease is caused specifically by influenza type A and type B viruses with the majority of infections caused by influenza A. Influenza B disease is more common in children and young adults and causes seasonal epidemics every 2-4 years (1). Influenza B is composed of two genetically distinct lineages: B/Victoria and B/Yamagata which have been co-circulating since the late 1980s (2). This now poses a frequent challenge for stakeholders when deciding the composition of the annual trivalent vaccine which contains A/H1N1, A/H3N2 and either one of the B virus lineages. Because there is no antigenic cross reactivity between B lineages there is often mismatch between the vaccine composition and the circulating B virus of the forthcoming season because the current selection system relies on chance. Indeed, for 5 of the 10 US influenza seasons between 2001 and 2010 little or no B virus protection was provided by the available vaccine (US CDC data).

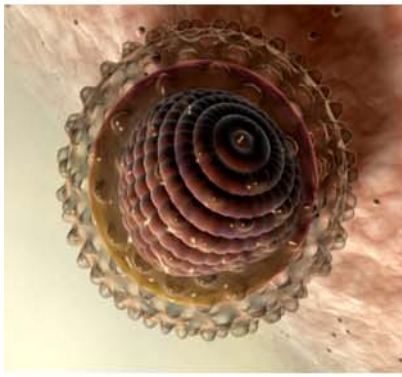
In order to reduce B virus mismatch of the influenza vaccine the concept of a quadrivalent influenza (QIV) vaccine containing both B/Victoria and B/Yamagata components has now progressed. This evolution of the influenza vaccine can be likened to the switch from bivalent (A/H3N2 and B) vaccines to a trivalent format (A/H3/N2 + A/H1N1 + B) in 1977 again due to lack of cross protection between A/H3N2 and A/H1N1 (3).

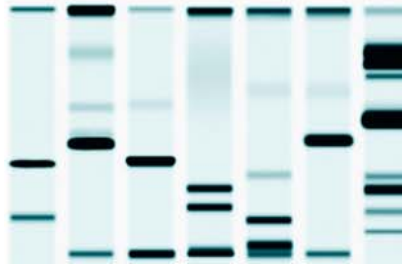
The benefit of a QIV vaccine would be mainly twofold: firstly, the vaccine would provide a direct benefit to recipients during a season with vaccine mismatch or significant B virus co-circulation and secondly, future benefit in subsequent seasons by providing accumulated immunity to both B virus lineages. The latter point is particular important because it has been shown *via* serologic studies that children accumulate natural immunity to influenza B more slowly than to influenza A (4). This could partly explain an increased incidence of B illness relative to influenza A in this age group.

A recent CDC analysis has estimated that the widespread use of QIV vaccines would result in a range of 2,200 – 970,000 fewer cases of influenza illnesses each year, 14-8,200 fewer influenza-associated respiratory hospitalizations and 1-485 fewer influenza related respiratory deaths (5). In cumulative terms this would have saved 1,200 lives for the US 2001-2008 seasons.

The development of QIV vaccines is close to the stage of commercial availability with AZ/MedImmune, the pioneer of Western live-attenuated influenza vaccines (LAIVs) back in 2003, gaining FDA approval for the first QIV LAIV (FluMist® Quadrivalent) in late February 2012 (6) MedImmune's pivotal study for was conducted in 2312 children aged 2-17 yrs (Identifier: NCT01091246) which started in March 2010. The QIV vaccine's basis for licensure was the demonstration of efficacy through non-inferiority of HAI antibody responses compared to trivalent FluMist® and the demonstration of comparable safety. The vaccine is expected to be ready for the 2013-2014 US seasons.

Other major influenza manufacturers are also developing QIV vaccines. World leader in terms of production volume, Sanofi Pasteur has recently released new Phase III data at the Annual Meeting of the Pediatric Academic Societies in Boston in children 6 mos through 8 years of age (n=4,300) (7). In March 2012 GSK Biologicals also submitted to US (sBLA) and EU regulatory authority's applications seeking approval of its quadrivalent influenza vaccine (GSK2282512A). The vaccine is indicated for the active immunisation of adults and children from 3 years of age (8).





Novartis Vaccines have published data regarding a dose-ranging study in 480 healthy children 6 to <36 months of age with an investigational QIV vaccine **(9)**. Study data were collected between October 2008 and March 2009 in 10 centers in Finland and 5 centers in Belgium. However, according the official Novartis Vaccines pipeline a QIV approach does not appear to be in late stage clinical development.

Key questions regarding potential uptake and global commercialization of QIV vaccines have been recently addressed **(10)**. In light of the multitude of company lifecycle management initiatives for influenza vaccines e.g. intradermal, high dose, cell culture, adjuvantation it is tempting to speculate that QIV vaccines could become yet another niche offering overshadowed by trivalent (TIV) products which dominate the approximate 500-600m doses distributed each year globally for seasonal influenza. Uptake of QIVs will largely depend on recommendations put in place firstly by the US ACIP and the extent of harmonization with the US stance by other national decision making bodies.

Naturally, the incremental increase in price levied by manufacturers will largely affect the extent of global QIV uptake, especially within cost conscious public markets where the majority of vaccine volume is consumed. Switching to a more complex production method provides many arguments in favour of manufacturers in their pricing negotiations.The addition of a fourth virus strain to influenza vaccines probably confers more clinical benefit than all of their previous enhancements observed so far. The question(s) are how much do buyers believe that extra benefit is worth and how much are manufacturers willing to push for a full switch to the QIV approach.

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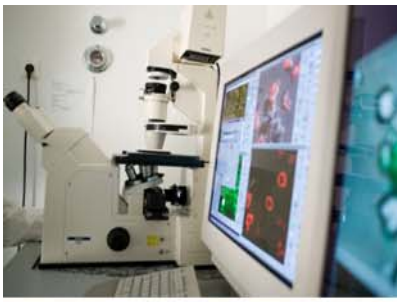

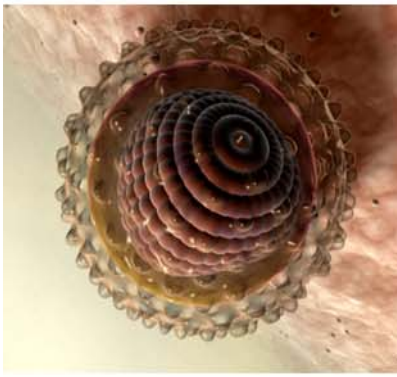

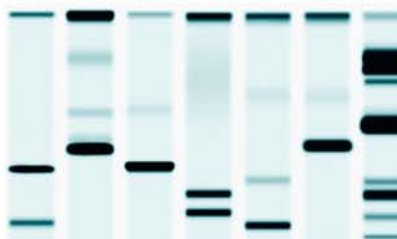

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