H1N1 vaccines – the pros and cons of new technology

LONDON, UK----13th October 2009----ExpertREACT. The urgency to contain the first influenza pandemic for decades coupled with intense competition amongst manufacturers has delivered a plethora of H1N1 vaccines in almost record time, some with relatively untested technologies. Deciding which H1N1 vaccine is appropriate for each risk group against the backdrop of seasonal vaccination will be a challenging but unavoidable task.

In the latest update (number 69) regarding H1N1 pandemic influenza, the World Health Organisation (WHO) stated there had been around 375,000 confirmed cases and over reported 4500 deaths globally (1). In reality the number of cases is likely to much higher and set to increase as the Northern Hemisphere moves into the winter months when seasonal influenza usually peaks in incidence. The WHO states that in many Northern hemisphere countries, the national level of ILI (influenza-like illness) is higher than baseline levels normally experienced for this time of year. In the Southern hemisphere, where transmission is now declining, H1N1 impact remained variable with selected regions such the Caribbean having experienced high levels of respiratory disease.

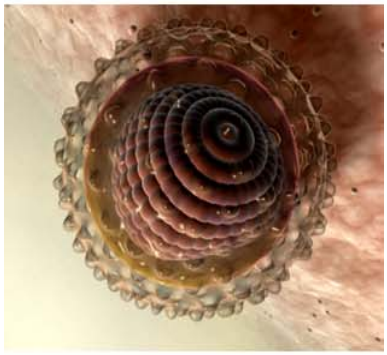
Numerous governments are now preparing for mass vaccination campaigns with new H1N1 vaccines to protect the most vulnerable members of their population. Back in August, the US ACIP published recommendations on use of the vaccine and set out "initial target groups" and "priority groups" for allocation purposes (2). Persons in the larger "initial target groups" allocation were estimated to number 159 million, and in common with seasonal flu, recommendations were skewed toward the immunocompromised and pregnant mothers. Unlike seasonal flu, a focus is placed on younger healthy persons (6 mos – 24 years) rather than the elderly (>65 yrs) reflecting current disease epidemiology and rates of hospitalization. Other large Western nations have published similar recommendations with slight variances on age ranges.

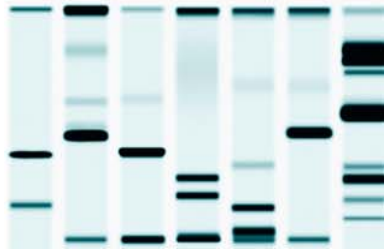
In the terms of commercial vaccine manufacturers, progress has been surprisingly rapid. The H1N1 vaccine has certainly proved more amenable than for example, H5N1 vaccines which were poorly immunogenic. GSK (Pandemrix), Sanofi Pasteur (Panenza, Humenza), Novartis (Focetria, Celtura), Medimmune (Flumist) and Baxter (Celvapan) have either gained vaccine licensure or positive regulatory opinion. Noticeable trends reflect those observed in seasonal flu where the US environment tends to favour more traditional vaccine approaches and suppliers.

What is less surprisingly than the rapid progress observed in H1N1 vaccine development is the intense competition amongst manufacturers who clearly are taking the ongoing battle from seasonal flu and extending it into H1N1. **VacZine Analytics** observes the three usual agendas being pushed: **1)** The use of cell culture technology **2)** The use of new adjuvants – which is helping manufacturers minimize the number of doses per course and **3)** Age group indication.

Contrary to early expectations that the H1N1 vaccine would require 2 doses (due to immunologically naivety) (2), clinical trial data from GSK Biologicals and Sanofi Pasteur suggest 1 dose may be sufficient to provide a protective immune response in all age-groups, even without an adjuvant in the case of the Sanofi Pasteur vaccines (3). The Sanofi data observed with Panenza and Humenza is especially interesting since GSK Biologicals, a relative newcomer to a large scale influenza focus, has pushed strongly the inclusion of AS03 (MPL-containing) adjuvant in Pandemrix gaining orders of around 440 million doses (4). In effect, Sanofi could potentially neutralize GSK's perceived advantage by also proving their vaccines could be single dose. Ironically, it is most likely GSK who prompted otherwise traditional Sanofi Pasteur to increase focus on their novel adjuvant AF03. The EU authorities remain more receptive to H1N1 vaccines with novel adjuvants while the US reserves their usage under emergency use authorization (2).

Novartis Vaccines and Baxter are focusing on cell culture technology in their H1N1 strategies. Baxter received EU Commission approval for CELVAPAN, October 7th and notably is the second vendor, along with GSK on the UK government contract. The company also states that CELVAPAN may be amenable to one dose also although the vaccine is focused on >18 yrs only.





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Novartis Vaccines appears to be stretching novel influenza vaccine technologies the furthest with investigation of Celtura that contains both a cell culture derived antigen AND a novel adjuvant, MF-59, also found in their EU seasonal product, FLUAD. Again in the >18 yrs group, Novartis showed in a pilot trial that Celtura could induce protective antibodies in 80% of subjects (n=100) with one dose and 90% with two doses **(5).** Interestingly, Novartis' seasonal cell culture vaccine, Optaflu still is not approved in the US although gaining EU positive regulatory opinion in 2007.

With so many H1N1 vaccines now potentially on offer, some commentators point to the possibility of "doubt and confusion" as campaigns initiate in the Northern hemisphere. Part of this will arise from the fact that the H1N1 vaccine will need to be given alongside seasonal vaccines, but also because groups such as pregnant women are being prioritized. For example, there is currently no data regarding the use of GSK's Pandemrix in pregnant women **(6).** In practice it will be the decision of national authorities to decide which particular vaccine is offered to which particular risk group, and the number of doses/timing of vaccination.

Commercial competition in influenza has undoubtedly increased the number of available options and despite potential price erosion has recently has attracted more development companies with a flurry of recent flu-related acquisitions e.g. Abbot (Solvay), Johnson & Johnson (Crucell) & Merck Co (CSL, Afluria). From a purely medical and safety perspective, it is tempting to point out that commercial agendas i.e. the inclusion of novel adjuvants may not be fully appropriate for the biggest public health concern, since possibly the emergence of HIV in the early 1980s. Indeed many in the US will focus on the US 1976 "Swine flu" as a case study. However, with the reported emergence of sporadic H1N1 resistance to oseltamavir and continued H1N1 mortality, one could counter by saying that commercial agendas and the quest for innovation have also delivered life saving vaccines faster than ever before.

References and Notes:

***Major Western markets are considered United States, United Kingdom, France, Germany, Italy and Spain*

1) World Health Organisation (WHO). Pandemic update no: 69. Available at: http://www.who.int/csr/don/2009_10_09/en/index.html. Accessed October 2009.

2) Use of Influenza A (H1N1) 2009 Monovalent Vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR. August 28,2009 / 58(RR10); 1-8

3) Sanofi Pasteur Corporate Press Release. October 8th 2009. Available at: http://www.sanofipasteur.com/sanofi-pasteur2/sp-media/SP_CORP/EN/54/964/H1N1%20Oct08%20VA.pdf?siteCode=SP_CORP. Accessed October 2009.

4) GSK Corporate Press Release. September 2009. http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10089.htm. Accessed October 2009.

5) Novartis Corporate Press Release. September 3rd 2009. Available at: http://www.novartis.com/newsroom/media-releases/en/2009/1339223.shtml. Accessed October 2009.

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