

Live Attenuated Swine Influenza Vaccine for Children Safety in Question

The live attenuated swine flu vaccine intended for millions of children has dangerous side effects and is genetically unstable, risking generation of new pandemic strains should mass vaccinations go ahead. [Prof. Joe Cummins](#) and [Dr. Mae-Wan Ho](#)

This report has been submitted to Sir Liam Donaldson, UK Chief Medical Officer, & to the US Food & Drug Administration Please circulate widely, with all hyperlinks included, to your elected representatives and public health departments.

The swine flu vaccines being prepared for release to combat the current pandemic will be fast tracked without the usual clinical trials to ensure their safety. Five different companies were contracted to produce vaccines worldwide - Baxter International, GlaxoSmithKline, Novartis, Sanofi-Aventis and AstraZeneca - using a range of technologies from traditional chicken egg production to cell culture [1] ([Fast-tracked Swine Flu Vaccine under Fire](#), SiS 43).

Most of the vaccines will not contain live virus and will be delivered by injection. However AstraZeneca will produce a genetically engineered live attenuated vaccine through its global biologics unit, MedImmune, using cell culture or eggs [2]. The MedImmune vaccine will be used primarily for children, to be delivered as a nasal spray. The nasal spray vaccine against pandemic H1N1 influenza has been fast tracked for global distribution [3].

The live-attenuated vaccine appears more effective than the inactivated virus vaccine, but it resulted in significantly higher rates of severe adverse events. Furthermore, there is evidence that the live vaccine is highly genetically unstable in warm body cells and that has not been thoroughly evaluated in the children vaccinated.

Live attenuated versus inactivated influenza vaccine

MedImmune sponsored a safety and efficacy trial of the nasal spray live- attenuated, cold adapted (see below) influenza vaccine compared with inactivated vaccine on infants and young children 6 to 59 months of age [4]. The study was conducted at 249 sites in 16 countries; US (49 % of subjects), 12 countries in Europe and Middle East (45 %), and 3 countries in Asia (6 %).

A total of 7852 children completed the study. The results showed that there were 54.7 % fewer cases of culture-confirmed influenza in the group that received live attenuated vaccine than in the group that received inactivated vaccine (153 cases, 3.9 % vs 338 cases, 8.6 %). For all culture-confirmed symptomatic influenza (both vaccine and non-vaccine strains), the overall attack rates were 5 % in the group that received live attenuated vaccine and 10.0 % in the group that received inactivated vaccine, indicating that neither vaccine was particularly good at preventing illness from non-vaccine strains. These results broadly confirm those of a comprehensive review carried out in 2006-2008, which could not provide safety analysis [5].

It is important to note that the MedImmune study explicitly excluded children with a history of hypersensitivity to any component of the live attenuated vaccine or the inactivated vaccine, *known immunosuppressive condition, medically diagnosed or treated wheezing within 42 days before enrolment, a history of severe asthma*, body temperature higher than 37.8 C within 3 days before enrolment and the use of aspirin or salicylate-containing products within 30 days before enrolment. The conditions italicized are precisely those considered especially at risk from swine flu and identified as 'priority groups' for receiving the vaccine by the UK government, which intends to vaccinate the entire UK population starting in October [6], and there is already evidence that the inactivated flu vaccine tripled the risk of severe events in children with asthma [7]. These findings are confirmed in the Medimmune study, which exposes the highly inadequate safety considerations in the UK government's mass vaccination programme.

The results showed that among previously unvaccinated children,

wheezing within 42 days after the administration of dose 1 was more common with live attenuated vaccine, primarily among children 6 to 11 months of age, which had 12 more episodes of severe wheezing (3.8 %, compared with 2.1 %, $p=0.076$). Furthermore, rates of hospitalization for any cause during the 180 days after vaccination were significantly higher among the recipients of live attenuated vaccine who were 6 to 11 months of age (6.1 % compared with 2.6 %, $p = 0.002$).

The authors stated [4, p. 694]:“Until additional data are available, the observations related to medically significant wheezing and rates of hospitalization will restrict the use of live attenuated vaccine in children younger than 1 year and in children 12 to 47 months of age who have a history of asthma or wheezing.”

With that proviso, perhaps, they concluded that an “evaluation of the risks and benefits indicates that live attenuated vaccine should be a highly effective, safe vaccine for children 12 to 59 months of age who do not have a history of asthma or wheezing

Immunizing school children finds favor with governments because it provides herd protection for the population and is considered more effective than immunizing elderly and high-risk patients [8]. The MedImmune nasal live attenuated influenza vaccine for seasonal and pandemic influenza is called FluMist.

Producing live attenuated influenza vaccine

Influenza virus infection depends on two genes coding for haemagglutinin (HA) and neuraminidase (NA). HA and NA are on the surface of the virus, and are therefore targets for vaccination. Because classical reassortment methods (see [1]) for producing influenza vaccine are time-consuming and cumbersome, a new, more efficient and faster “reverse genetics” method was devised that assembles RNA virus from the genes on DNA plasmids. For vaccine production, eight plasmids -containing the HA and NA genes from pathogenic influenza strains plus six genes from a non pathogenic master strain - along with additional plasmids encoding proteins necessary for replication and transcription, are transfected into cell lines [9]. Virus can

then be harvested from these cells for the production of inactivated or live attenuated vaccine. Live attenuated influenza vaccine (LAIV) was originally derived by cold adaptation of an influenza type A strain by serial passage at sequentially lower temperatures in chick kidney cells. During that process, multiple gene mutants were selected for cold adapted (ca), temperature sensitive (ts) and attenuated (att) phenotypes of master donor viruses (MDVs). The MDVs represent the live attenuated virus backbone that are updated for annual influenza or pandemic influenza HA and NA genes from disease strains. The vaccine seed strain selected in the process is then used to produce quantities of live attenuated vaccine. No preservatives are added to the vaccine produced from the vaccine seed strain [10].

The Madin-Darby canine kidney (MDCK) cell line was chosen to produce quantities of live attenuated influenza vaccine (LAIV). The MDCK cell line was compared with the Vero cell line derived from kidney epithelial cells of the African green monkey and other cell lines derived from foetal lungs of humans or Rhesus monkey. Both MDCK and Vero cell lines supported high-level production of LAIV for some strains of the virus while the other cell lines were less productive. However, only the MDCK cells produced quantities of all of the LAIV strains [11].

Problem with genetic instability of LAIV

LAIV replicates primarily in the ciliated epithelial cells of the nasopharyngeal mucosa to induce mucosal immune responses. LAIV viruses do not replicate well at the warmer temperatures found in the lower airways and lung. In the course of replication, all LAIV viral proteins would be presented to the immune system in their native conformation and the resultant immune responses mimic those of natural infection with influenza virus [10].

A potential problem was observed in studies of LAIV as it encounters restrictive temperature in the lung. The viral polymerase function is reduced and virus replication, assembly, and release become impaired [12]. The morphology of the temperature-restricted virus was affected and the virus particles contained high levels of heat shock protein. Impairment of the viral replicase is a matter of concern because replicase may

create new pandemic strains. Restrictive replication of LAIV at the restrictive temperature occurs in multiple steps in the virus replication cycle [13]. Shedding of LAIV is observed in individuals between 5 to 49 years of age up to 11 days after vaccination, and vaccinated individuals were advised to avoid contact with severely immunosuppressed individuals for a week after vaccination [14].

Millions of children may soon be vaccinated with LAIV. But there is a large deficit in scientific studies on the molecular biology of LAIV exposed to restrictive temperature. The restricted viruses are genetically unstable and may result in gene alterations that serve to seed pandemic strains of influenza. This possibility must be thoroughly investigated before we expose millions more people to such live viruses.

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