

## FluMist immunization and Primary Immunodeficiency

Testimony presented at the May 16, 2007 meeting of the Vaccines and Related Biological Products Advisory Committee of the FDA that was considering an application by the manufacturer, MedImmune, to lower the minimum age of immunization of children with FluMist from 60 months to 12 months of age.

The Immune Deficiency Foundation (IDF), founded in 1980, is the national patient organization dedicated to improving the diagnosis and treatment of patients with primary immune deficiency diseases (PIDD) through research, education and advocacy. In the United States, approximately 250,000 people are diagnosed with primary immune deficiency diseases. Thousands more go undetected. These diseases are chronic illnesses caused by hereditary or genetic defects in the immune system in which part of the body's immune system is missing or does not function properly.

There are over 130 primary immune deficiency diseases and they affect people differently. For some, the body fails to produce any or enough antibodies to fight infection; while for others, the cellular defenses against infection fail to work properly. Throughout their lives, people with primary immune deficiencies are more susceptible to infections, endure recurrent health problems and often develop serious and debilitating illnesses.

IDF recognizes the importance and enthusiastically supports the development of new vaccines to help protect the general population, and -- by way of herd immunity -- those patients with inherited defects in the immune system.

**However, we also want to emphasize that evaluation of the potential risks of live agent vaccines to patients with defects in immunity must be part of the development and approval process for these vaccines.**

Over the years many, many patients with primary immunodeficiency diseases (PIDD) have had serious or even fatal infections with live vaccine agents including the oral polio vaccine, BCG, varicella, measles and vaccinia.

These agents are typically recognized to be a threat to those individuals carrying a diagnosis of primary immunodeficiency and appropriate cautions are usually included in

the drug package insert materials. However, surveys indicate that the average time from onset of symptoms of PIDD to establishment of a proper diagnosis is 9.2 years. Therefore, many individuals at potential risk from live agent vaccines (and their physicians or others delivering the vaccine) will be unaware that there is a potential problem.

*The IDF urges that when recommendations for immunization with new live agent vaccines are being developed by manufacturers, the FDA and CDC, that consideration be given to include a warning statement to alert physicians to avoid use of these agents in patients that may have unrecognized immunodeficiency until appropriate studies have ruled out that possibility. These warnings should indicate that the vaccine be withheld from individuals that have experienced recurrent, persistent, severe &/or unusual infections, particularly if others in the family have a similar susceptibility to infection.*

*Further, the IDF believes that investigation of the susceptibility of immunodeficient subjects to SAE from live vaccines and exploration of strategies for treating disease caused by live agent vaccines should be considered as an integral part of the drug development and approval process for these materials.*

Several live agent vaccines are known to have some capacity for horizontal spread to unimmunized contacts – a property that may be useful to ensure greater efficacy in developing herd immunity – but a property that provides yet another risk to potentially susceptible individuals with PIDD. As more and more live agent vaccines are entering the market place – and as some are being adopted for immunization programs to be administered in the schools– the risk that a susceptible individual may receive such live vaccine agents increases. Frequently parents of immunodeficient children ask us for advice about what they should do if a patient’s healthy sibling or playmate must be immunized with a live agent vaccine? “Do we keep our child out of school for 3 weeks?” “Do we send the newly immunized sibling to live with relatives for a month?” These are real concerns and thought to their answer is an important part of your deliberations.

Severe combined immunodeficiency (SCID) is generally the most serious of the PIDD, and infants born with this disease usually die of infection within the first year. Deaths from both influenza A and B have been seen in this patient group. SCID infants appear normal until they become infected, accounting for the fact that the mean age of diagnosis of SCID in the largest U.S. series was 6.5 months of age. Since newborn screening for this condition is currently not being carried out, these infants will continue to receive live agent vaccines scheduled as part of the routine immunization of all infants. SCID represents a true pediatric emergency since the cure rate using bone marrow transplantation is as high as 96% if the procedure is carried out by 3 months of age, before the infant acquires a serious infection. The success of marrow transplantation falls dramatically in already infected infants.

In countries where BCG immunization is routinely practiced, infants with severe combined immunodeficiency (SCID) regularly develop fatal BCGosis from the vaccine that is often administered before the diagnosis has been established. Similarly paralytic polio has developed in patients with agammaglobulinemia and also in patients with SCID following administration of oral polio vaccine. Chicken pox immunization has resulted in fatal infection in SCID babies. Immunization with vaccinia has long been recognized to pose a very serious threat to patients with eczema and it has resulted in fatal infections in infants with SCID and other PIDD with T cell deficiencies like the Wiskott-Aldrich syndrome. Rotavirus is one of the infectious agents that routinely causes chronic persistent infections in infants with SCID. For the newly introduced vaccine, the current recommendations are to begin the course of immunizations with the live rotavirus vaccine at around 2 months – a time before most of these infants will be recognized to have a serious contraindication to receiving this live virus agent.

Concerning FluMist, no direct data on the risk posed to patients with PIDD is available. However there is some concern that by moving the minimum age of immunization with this live virus vaccine to still younger individuals that the risk of inadvertent administration to a toddler with a serious but not yet diagnosed PIDD will be increased. Clinical studies performed to date in children as young as 6 months have not disclosed

any unmistakable evidence that the agent will be dangerous, although none of these studies have been carried out in a setting comparable to what is seen in infants with severe combined immunodeficiency or other severe primary immunodeficiency diseases. Although horizontal transmission has been shown to occur in one study of young children in a day care center, its frequency was low (2%) and was not associated with disease in the recipients.

The IDF believes that on balance this agent - if used widely - will enhance protection of the immune compromised though better herd immunity. The temperature sensitivity built into the vaccine probably gives a margin of safety to the inadvertently immunized (or exposed) immune compromised patient. Following the "inadvertent" direct FluMist immunization of a severely immune compromised individual we are somewhat reassured by the knowledge that the agent is sensitive to Tamiflu and recommend initiating treatment with it as soon as possible after the exposure. Continued surveillance for development of SAE in patients with PIDD is essential to develop data on the actual risk to patients with this group of diseases and on the effectiveness of treatment with Tamiflu to any patient developing disease following FluMist exposure.