Trends-in-Medicine

December 2002
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SUMMARY

MedImmune's nasal spray flu vaccine got a positive recommendation from an FDA Advisory Panel, which makes it likely the product will be on the market for the 2003-2004 flu season. However, the panel recommended a narrower age range – 5 to 49 – than the company wanted, and MedImmune officials indicated they will try to convince the FDA to broaden this to include 50 to 64-year-olds.

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FluMist Moves a Step Closer to Market

On December 17, 2002, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the FDA's Center for Biologics Evaluation & Research (CBER) recommended approval of MedImmune's live, cold-adapted, nasal spray influenza vaccine, FluMist, for ***healthy*** people age 5 to 49. FluMist will be marketed by both MedImmune and Wyeth (which gets 35% of sales revenue).

Wyeth also recently announced it was ceasing production and sale of its inactivated flu vaccine, FluShield, as well as its injected pneumonia vaccine, Pnu-Imune. This leaves only two inactive flu vaccines on the market, Aventis's Fluzone and PowderJect's Fluvirin.

MedImmune officials appeared happy that the vaccine got a positive panel vote and were hopeful they could convince the FDA to do what the panel wouldn't – that is, approve the 50-64 age group as well as 5-49. The PDUFA action date is in February 2003.

FluMist 2002 Advisory Panel Vote

Question	Yes	No
SAFETY		
Age 5-17	17	1
Age 18-49	17	1
Age 50-64	10	8
EFFICACY		
Age 5-17	14	4
Age 18-49	17	1
Age 50-64	4	14

Even if the FDA approves FluMist only for individuals 5-49 years old, MedImmune's biggest problem is likely to be supply, not demand. Officials said the company can only make 6-8 million doses the first year – which probably will be the 2003-2004 flu season. MedImmune is planning to scale up production, but officials said this will require multiple FDA approvals and will take time. They declined to say how long it is likely to take the company to ramp up to 30-50 million doses per year. They also refused to discuss pricing.

FluMist was first submitted to the FDA in October 2000 by Aviron (which was later acquired by MedImmune), and this was the second time VRBPAC had considered it. In July 2001, the panel voted FluMist was effective but not safe:

FluMist 2001 Advisory Panel Vote

Question	Yes	No
SAFETY		
Ages 1-64	4	10
EFFICACY		
Children 1-17	8	7
Children 2-17	13	2
Adults 18-64	13	2

After that first panel, MedImmune submitted additional data, and that satisfied the second panel's safety concerns sufficiently for them to recommend approval for all requested age groups. FluMist has now been studied in a total of 20,228 healthy children, adolescents and adults through 20 clinical trials. Among the key trials of FluMist were:

- AV019 which studied 9,689 healthy children (age 1-17) in the Northern California Kaiser Permanente health plan.
- AV012, a study of 7,448 healthy children (18 months –18 years) in Texas.
- AV009, a study of 4,303 healthy people age 18-64
- AV006, a two-year study of 1,602 healthy children (15-71 months)

Among the efficacy concerns for the first panel were the number and timing of doses (children under 9 get two annual doses). The first panel's safety concerns were also raised at this second panel. A panel member summed up the issues pretty well during the discussion period, saying, "This vaccine does have an asthma problem in age <5, and that is borne out by the new analysis. With older individuals that is probably not the case. There is evidence of shedding and transmission, but I am somewhat relieved by the data today on transmission. The reassortment issue is still on the table. One issue we are facing is that this was a vaccine initially designed for young children, and now it is being reassessed and re-looked at for older groups, and the problem in some ages is lack of specific data on the specific vaccine. My concern is the 5-9 age group, but the data suggests in all likelihood it is safe in 5-17 year olds. Over age 50, there is a lack of numbers (of patients in the trials). But concerns about this vaccine remain."

Topics discussed at this panel included:

1. ***A potential increase among vaccine recipients in:***

- **The rate of asthma and the risk of exacerbation of asthma.** The FDA reviewer said, "The concern is ongoing for the risk of asthma/wheezing events in young children and subjects with a history of asthma." A MedImmune official said any asthma exacerbation in younger children is only associated with the first dose, not Dose 2 in younger or older children. A panel member said, "Asthma is a potential problem with children <5 and older age groups, but there is no data to know that what might be precipitated by FluMist is less than what would occur with natural infection." A doctor who served on both panels said, "Asthma has been identified as a potential problem in the <5 age group. I'm not convinced it's a problem, but the answer will come from more studies."

Asthma Events in AV019 Trial

Age	FluMist	Placebo	Relative Risk
12-59 months			
Dose 1	14/2020	2/1011	3.53
Dose 2	21/1728	8/861	1.31
60-107 months			
Dose 1	8/1748	5/858	.78
Dose 2	4/1514	6/739	.33
9-17 years			
Only 1 dose	11/2705	9/1347	.61

- **Flu-like illness in the days following vaccination**. A MedImmune official said, "FluMist is associated with mild URI symptoms in children and adults. There is no significant increase in acute influenza-like illness and no significant difference between the groups for fever >101°F following FluMist administration. Reactogenicity rates are lower following annual revaccination."
- **Pneumonia.** A MedImmune official said, "What we can say now is that FluMist is not associated with an increased risk of pneumonia in children or adults." The FDA reviewer concluded that, based on the new data, "There was no increase in pneumonia, bronchitis or bronchiolitis events post-vaccination."
- **Conjunctivitis**. A MedImmune official said, "We identified a temporal association in the first 14 days below 48 months; and for children 60 months - 17 years, there was an increased relative risk of 0.1%."
- **Nasal congestion.** The most common adverse event attributable to FluMist is runny nose/nasal congestion.
- **Other risks.** A MedImmune official said there is not any increased risk of CNS events, "In all the studies, we saw no cases of encephalitis, Guillian-Barre, Reye syndrome, or other rare disorders."

2. Limited safety data in the very young, those over 50, and people who are not healthy. The panel was particularly concerned with the lack of data on people over age 50. In fact, there was more safety data overall on FluMist than efficacy data, and that bothered some panel members. One doctor asked FDA officials, "How often do new products come to a panel when the question is efficacy and the data is on safety?" An FDA reviewer responded, "I can't think of any." Another panel member said, "I can't think of a biologically sound

reason that FluMist is not safe in the 50-64 age group." A third commented, "The data was barely adequate." A fourth said, "There was inadequate data for the 50-64 age group." A MedImmune official tried to reassure the panel, saying, "We clearly demonstrated efficacy in children and adults. There doesn't seem to be a biologically plausible reason for the middle group to have a different effect. The studies were just designed looking at specific issues. The issue of age 50-64 is a post-hoc fact…511 were in the trial. Our view is that…we demonstrated efficacy in children and adults."

Number of Subjects in the AV009 Adult Trial

Age (in years)	FluMist n=3041	Placebo n=1520
18 - 29	747 (16.4%)	375 (8.2%)
30 - 39	998 (21.9%)	486 (10.7%)
40 - 49	857 (18.8%)	457 (10%)
50 - 59	390 (8.6%)	181 (4.0)
60 - 65	49 (1.1%)	21 (0.5%)

3. ***No data on concomitant administration with other vaccines*** **(e.g., DtaP, MMR, and IPV in 4-6 year olds, and the pneumococcal vaccine in adults).** Concurrent immunization is excluded in the proposed label, but additional studies are being conducted to determine if this exclusion is really necessary. A MedImmune official said a trial is ongoing and fully enrolled with 1,251 patients of FluMist given concomitantly with MMRII and VARIVAX. He did not say when and where that data would be available.

4. ***Potential for genotype or phenotype reversion (reassortment).*** There were long and technical discussions of this issue. Panel members were worried the vaccine could mutate, but MedImmune officials insisted that no super-virus could or would arise. The FDA reviewer said, "Recovered vaccine viruses had a high frequency of nucleotide changes, which weren't random but the clinical significance of the changes was not known."

5. ***Limited data on re-vaccination.*** The safety and efficacy of repeat FluMist vaccinations, particularly in adults, worried several panel members. The only data on repeat administrations of FluMist are in children.

6. ***Efficacy of FluMist given to patients who previously had the inactivated vaccine.*** Does prior inoculation with the inactivated virus result in less viral shedding with FluMist? That was a question several panel members wanted to know, but the company couldn't answer. A panel member wondered, "Another thing is whether other populations get inactive vaccine and how that may impact outcomes from transmission of this (FluMist). That is important to know."

7. ***Lack of data in high risk patients.*** There was no data on high risk subgroups, except for one trial in HIV patients which did not show an increased risk with FluMist use, compared to non-HIV patients. A panel member said, "The HIV data helped a lot…but the absence of data on high risk patients is striking. My concern is that as (this) vaccine is used, there will be high risk people immunized inadvertently, either accidentally or because they don't know they are high risk because of underlying diseases."

8. ***Shedding and transmission of vaccine strains to contacts.*** The FDA reviewer said, "Shedding of vaccine virus was frequent, occurring in about 80% of patients, and lasted through Day 21. Transmission occurred, but the rate estimate is crude." A panel member said, "I'd like to know more about transmissibility, and I don't think the data we have addresses that because it is too small, but I agree that in moving it from protection of high risk individuals to healthy individuals, do we incur more problems than we solve in that setting? I think we need to address the safety of the vaccine. When I look at historical data on the persistence of the virus, there was little data for people over 50 about how long the virus is there and if it is transmitted in that population, and I think that is important." A MedImmune official responded, "It was not looked at but in one kid, we know the virus was transmitted." Another panel member said, "My concern was high risk individuals in households with healthy individuals who get this vaccine."

A Finnish day care study found that 80% of vaccine recipients (all children) shed vaccine virus for a mean of 7.6 days.

Challenge Study Results

Age	% Shedding	Mean duration of shedding
Children (1-17 years)	67% - 91%	4.5 - 9 days
Adults	14% - 60%	0.6 - 1.9 days

One panel member was not concerned with this issue but was unsuccessful in convincing his colleagues to end the discussion. He said, "It may seem gratuitous, but the…only other vaccine where questions of transmission has come up is the oral polio vaccine, and that was considered advantageous to transit from immunized to non-immunized individuals. Did anyone look at children who got the vaccine by transmission to see if they developed an immune response…We are spending all this time talking about transmission of attenuated virus. It is a matter of education, not science. All of the household contacts should have been immunized by inactivated vaccine, so the issue becomes moot if we have programs that work. We are losing perspective by focusing on transmission of attenuated virus. It is inappropriate to place such emphasis on attenuated virus."

A MedImmune official offered this additional information on transmission: Smaller studies found no transmission from

husband to wife – but they were not necessarily higher risk, though there have been high risk patients included in those studies.

- The factors affecting vaccine virus transmission are:
  - Frequency of virus shedding.
  - Level and duration of shedding.
  - Susceptibility of contact.
  - Intensity of contact.

- Probability of transmission is:
  - Expected to be lower in older children and adults.
  - Equivalent, at worst, to a FluMist vaccination in asthmatics as well as healthy individuals, though there may be a "low frequency" of wheezing exacerbation in the asthmatics.

- In immunocompromised individuals, temperature sensitive mutations limit it to URI, with prolonged virus shedding, but antivirals are available to treat them.

- The actual risk of something happening in the population:
  - *Assuming:*
    - Inoculum from transmission equivalent to vaccine dose.
    - Daycare transmission probability of 0.006.
    - Immunocompromised child has one FluMist contact.
    - Prevalence of immunocompromised contacts is 0.0015.
    - All fully immunocompromised at time of contact.
    - All in school.
    - Asthmas/wheezing risk in contact is 0.009 (equivalent to the risk observed in <60 month history positive children in FluMist study AV091.
  - *Then, the calculated risk would be:*
    - Estimated risk of transmission to an immunocompromised child in school = 0.000009.
    - Risk of an asthma/wheezing exacerbation attributable to a FluMist household contact=0.000054.
    - Likely to be >100 times lower in others.

Members of the second panel were satisfied with the FDA's plan for dealing with the approval of new strains of vaccine after FluMist is approved. The chairman commented, "I think the FDA plan is sound. I would pitch for annual monitoring of efficacy once the vaccine is deployed. One way to do that is in areas where we have flu surveillance and develop a case control technique to assess efficacy of the vaccine each year."

Members recommended the FDA require continuing safety studies relating to transmission, asthma, revaccination, high risk patients, and patients with lung diseases such as COPD. Several member also suggested a head-to-head study comparing FluMist to the current inactivated vaccine, but one panel member commented, "I don't think we made the pneumonia vaccines go head-to-head."

In terms of post-marketing studies, the panel suggested studies on revaccination safety and efficacy and asthma in children. A panel member said, "We need airway studies, so can give this to younger children who were the original targets of this vaccine."

Following are questions posed by panel members and the answers MedImmune officials provided:

Question: Do we know more than we did in 2001 about the distribution of the vaccine, and is there any information about virus presence in the lower respiratory track?
Answer: "We've done radiation surveys of various components of the abdomen and have shown that the vast majority (of FluMist) ends up in the upper airway. In the lungs we see what we think is just background radiation from the esophagus where some vaccine is swallowed…If you use nasal drops you see the same amount of radiation in the lungs. We don't believe there is much of this (FluMist) that gets to the lungs, and given its temperature sensitivity, we would expect very little replication in the lungs."

Q: Why do children shed more virus?
A: Because of a lack of immunity. Children shed about 100 times more virus than adults.
Q: Will children grow up to be adults that shed more virus?
A: No, as they get immunity, they will shed less virus.

Q Stephens: What about resassortment, which is more a concern with wild type?
A: During a pandemic period there is a lot of reassortment going on…and if -- and only if -- an immunized individual also has a wild type infection at the same time, then you can get reassortment between FluMist and that strain. But at worst what you get back out is a wild type strain…So, in terms of normal epidemics, the risk of generating a super virulent strain is virtually impossible because the genes we have in FluMist are attenuated.

Q: Would it be possible for reassortment to, for example, produce a virus that is cold adaptive, no longer attenuated and no longer temperature sensitive?
A: No, then you would get the wild-type back.
Q: But wild-type is not cold-adaptive?
A: Actually a lot of them are cold-adaptive and temperature sensitive…There are 4 different genes for attenuation. If any of them ended up in the wild-type virus, it would attenuate it.

Q: What are your long-term plans for the 12-49 month age group?
A: We have fully enrolled that trial. We have other trials designed to look at other vaccine components – in combination with all the other childhood vaccines. We also have to go back and look at the asthma issue. We are talking to Kaiser to see if there are better ways to identify asthma positivity other than parental classification.

Q: Any thoughts on the over-64 group?
We are focused on healthy people in that age group for which FluMist could enhance uptake (of vaccination). Once we study that, we would like to study FluMist in higher risk populations, including the elderly.

Q: It appears COPD patients would be an obvious target. Have they been studied?
The only studies of COPD were at the VA and not presented here. (NOTE: The VA study also included unhealthy adults, but the numbers were too small to draw conclusions."