An expanded comment on the use of FluMist® for children and adults

Walter R. Schumm, PhD
School of Family Studies and Human Services
Justin Hall, Kansas State University
1700 Anderson Avenue
Manhattan, KS 66506-1403 USA
Phone: +1 785 539 3641 (home) +1 785 532 1494 (office)
Fax: +1 785 532 5505
Email: Schumm@ksu.edu (work) WRSchumm@aol.com (home)
Submitted: December 4, 2004 Accepted: January 14, 2005

Abstract

Recent disclosures of ethical lapses in medical research have heightened concern that the public be accurately informed of the benefits and risks of medical procedures and pharmaceutical agents. Statistics from the package insert for FluMist® were reanalyzed to check their accuracy. While a few minor errors may have been detected, the overriding issue is that FluMist® does not appear to reduce a person's chance of becoming ill during the annual flu season, only of reducing their chances of becoming severely ill from the flu itself. Such information should be provided to patients to allow them to make informed choices about their prospective medical procedures.

Keywords: Flu vaccine, FluMist®, informed consent, medical ethics

1. Background

The initial shortage of influenza vaccines reached even to the heartland of the United States. Even in my hometown of Manhattan, Kansas, stores had been posting signs that their pharmacies did not have any supplies of flu vaccine. The shortages of flu vaccine had increased concerns about the risks of the upcoming flu season in the United States and elsewhere. One possible solution to the overall shortage of vaccine was the use of FluMist® which is administered nasally rather than by injection. The prescribing information for FluMist® is available, as a package insert (circular) at http://www.FluMist.com/pdf /prescribinginfo.pdf.

The accuracy of pharmaceutical claims has been subject to much recent criticism [1,2]. In particular, there have been concerns about an exaggerated role of marketing [3] and of attempts to suppress "inconvenient findings" [4].

2. Method

Given those concerns and the importance of alternative flu treatments, information in the FluMist® circular was reviewed and the original data was recreated so it could be subjected to statistical analyses, primarily using Fisher's Exact Test. Two-sided Fisher's Exact Tests were used unless the direction of the effect was clear from the context of the package insert [5].

3. Results

Some discrepancies were observed.

In Table 1 of the circular, the efficacy of the vaccine in year one of testing is cited at 87.4%, with only 3 (1.8%) of 163 FluMist® recipients (children 60-71 months old) coming down with culture-confirmed influenza over the flu season compared to 11 (14.7%) of 75 placebo children. Similar results occurred for the second year of the testing, with 1.9% of the treatment group and 14.2% of the control group having culture-confirmed influenza. However, it cannot but be noted that even in the Placebo groups for both years, over 85% of the subjects never came down with culture-confirmed influenza despite the relative lack of vaccine protection. The results for years one and two are cited as being statistically significant ($p < 0.05$), but are in fact by Fisher's Exact Test more significant ($p < 0.001$).

Turning to Table 2 in the package insert, the effectiveness of FluMist® was examined for a treatment group of 2,411 adults and a control group of 1,226 adults. The insert correctly acknowledges that in terms of preventing any febrile illness, the vaccine was not significant. The actual significance level was just under $p < 0.10$ by Fisher's Exact Test. For severe febrile illness and for febrile upper respiratory illness, the results were significant as indicated, with $p < 0.02$ and $p < 0.006$, respectively by a one-sided Fisher's Exact Test. However, the amount of variance explained in both situations was, respectively, only 0.144% and 0.194% (obtained by squaring the Pearson correlations of 0.038 and 0.044). Even though the amount of variance explained was trivial, the percentage reduction in illness appeared to be substantial, at 19.5% and 23.7%, respectively.

Of more concern are the results regarding adverse events observed within ten days of each dose, reported in Table 3 of the circular. A note underneath the table says that "There were no statistically significant differences in any of these events (p-value > 0.05); Fisher's exact method." However, headache was observed for 6.8% of 161 children who received FluMist® compared to 16.0% of placebo subjects, a difference significant

doi: 10.1588/medver.2005.02.00040

by Fisher's exact test ($p < 0.04$, two-sided). Runny nose/nasal congestion was observed for 46.0% of the treatment group compared to 32.0% of the placebo groups, again a difference significant by Fisher's exact test ($p < 0.05$, two-sided). Combining all events together to create "any event," 66.5% of the treatment group versus 53.3% of the placebo group had at least one adverse event, a difference nearly significant by a two-sided Fisher's exact test ($p = 0.061$) and significant by a one-sided test ($p < 0.04$). In contrast to the note under Table 3 of the circular, at least some of the statistical tests were significant ($p < 0.05$). It is possible that the circular's author(s) used Bonferroni procedures to reduce the alpha level for each test, but if they did so, they did not make that clear. In fact, the insert says that "There were no statistically significant differences in any of these events," which appears to imply each event was considered by itself. However, if we make the best possible case for FluMist® and accept 66.5% adverse events (107 of 161) for the treatment group of children but no flu cases and 68.0% adverse events and/or flu (40 events and 11 flu cases, 51 of 75) for the placebo group, we find no significant differences between the two groups in total health outcomes by Fisher's exact test ($p = 0.882$, two-sided). Because of the smaller sample size used for testing the vaccine among children, the amount of variance explained, though not statistically significant, accounts for more than in the previous adult samples. For example, in Table 3 of the insert, 17.8% of the treatment group reported headaches within 10 days after taking the vaccine compared to 11.6% of the control group. That difference was not quite significant statistically ($p < 0.12$) but was associated with a Pearson correlation of 0.078, which would explain 0.608% of the variance between being vaccinated and having headaches within ten days of vaccination. Though small, that amount of explained variance is still much larger than that noted previously for a statistically significant result.

The situation for adults is similar. As noted previously, Table 2 in the insert indicates that 8.8% of treatment group adults (18-49 years old) experienced a febrile upper respiratory illness compared to 11.6% of placebo adults ($p < 0.05$). However, with respect to "any febrile illness," the differences between treatment group (13.7%) and the placebo group (15.4%) were not significant ($p > 0.05$). Table 4 indicates that 71.9% of treatment group adults experienced "any event" within 7 days of each dose compared to 62.6% of placebo group adults ($p < 0.05$). Coupled with the flu estimates as was done for the analysis of the children's data, 71.9% of the treatment group had some adverse health outcomes (events) compared to 74.2% (62.6% + 11.6%) of the placebo group. Even bending over backwards to benefit the treatment group outcomes, the net result is barely more than a two percent difference (74.2 – 71.9 = 2.3%) in adverse health outcomes between the treatment and control groups.

4. Discussion

The above results appear to indicate that FluMist® may be a valuable vaccine for children and adults most at risk of complications, especially severe complications, from an attack of an influenza virus, but the value for healthy children and adults with strong immune systems and with unrestricted access to effective health care systems may be subject to debate. Perhaps of even greater concern is the fact that the statistical information presented to health care professionals in the FluMist® circular is either incorrect or incompletely stated. In addition, important and substantial claims are being made for a vaccine's effectiveness, when the scientific amount of variance being explained can only be described as trivial. Nor does the information highlight the combined outcomes experienced by subjects, which would be useful for physicians trying to understand the overall advantages and disadvantages of using a particular vaccine.

Such issues further complicate discussions concerning the credibility of information provided by drug companies as it may impact adversely the recommendations of medical personnel and the decisions of patients.

References

[1] Roehr, B. Stronger sanctions needed against companies that suppress data. BMJ 2004, July 17;329:132.
[2] Lenzer, J. FDA's counsel accused of being too close to drug industry. BMJ 2004, July 24; 329:189.
[3] Kmietowicz, Z. Consumer organizations criticize influence of drug companies. BMJ 2004, Oct. 23; 329: 937.
[4] Editorial Board. The whole truth: drug companies must tell us all they know about the medicines we take. New Scientist 2004, May 1; 182(2445):3.
[5] McKinney WP, Young MJ, Hartz A, Lee MB. The inexact use of Shier's Exact Test in six major medical journals. JAMA, 1989;261:3430–3

Note: This article represents an expanded version of an electronic letter previously published by British Medical Journal: Schumm WR. A comment on the use of FluMist® for children and adults. BMJ, [electronic Letter], 2004. Available at http://bmj.bmjjournals.com /cgi/letters/329/7477/1253#87877 (Dec. 2/3, 2004).

doi: 10.1588/medver.2005.02.00040