



available at www.sciencedirect.com



journal homepage: www.elsevier.com/locate/vaccine



Inactivated influenza vaccine (IIV) in children <2 years of age: Examination of selected adverse events reported to VAERS after thimerosal-free or thimerosal-containing vaccine

A.W. McMahon^{a,*}, J.K. Iskander^b, P. Haber^b, M.M. Braun^a, R. Ball^a

^a Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, USA

^b Immunization Safety Office, Centers for Disease Control and Prevention, USA

Received 24 August 2007; received in revised form 26 October 2007; accepted 29 October 2007

KEYWORDS

Influenza vaccine;
Adverse event;
Thimerosal;
Infant

Summary Thimerosal as a preservative (in all but trace amounts) was removed from vaccines used in infants starting in the late 1990s, though the preservative-including inactivated influenza vaccine is still available for use in individuals ≥ 6 months of age. We compared the proportion of injection site reactions, rash, and infections reported to the Vaccine Adverse Event Reporting System (VAERS) after preservative-free (PFV), preservative-including (PIV), and preservative unknown (PUV) vaccines in reports from 7/1/2004 to 1/4/2006. There were 145, 175, and 216 reports after vaccination with PFV, PIV, and PUV, respectively. The most frequently reported coding terms (fever, rash, and urticaria) were seen in similar proportions in the PFV, PIV, and PUV groups. No difference was detected in the proportion of injection site reactions (ISR), rash, or infections in the PIV, PFV, and PUV reports. Keeping in mind the inherent limitations of VAERS, including underreporting and potential reporting biases, we conclude that there were no substantial differences in the proportion of rash, ISR, and infection reports in the PIV, PFV and PUV reports in infants.

© 2007 Elsevier Ltd. All rights reserved.

Introduction

Thimerosal is an organomercury compound derived from ethyl mercury, in use since the 1930s as a preservative in many vaccines licensed and marketed in the United States [1]. Thimerosal is metabolized in the body into ethyl mercury and thiosalicylate. Because of the theoretical potential for neurotoxicity of even low levels of organomercurials [2–5] and because of the increased number of thimerosal

* Corresponding author. Present address: Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Avenue, Room 3474, Silver Spring, MD 20993, USA.
Tel.: +1 301 796 1784; fax: +1 301 827 5218.

E-mail address: ann.mcmahon@fda.hhs.gov (A.W. McMahon).

containing vaccines that had been added to the infant immunization schedule in the early 1990s, a joint statement by the US Public Health Service and the American Academy of Pediatrics was issued 9 July 1999 recommending that thimerosal be reduced or eliminated from vaccines [6,7]. As of 7 March 2001, thimerosal had been removed from or reduced to trace amounts in all vaccines routinely given to children <24 months of age.

In 2001, the Food and Drug Administration (FDA) approved a preservative-free (<1 µg of mercury/0.5 mL) influenza vaccine [Fluvirin (Novartis, formerly Chiron/Evans) (preservative-free)], for use in persons 4-year of age and older. In 2004, a thimerosal-free influenza vaccine product (0 µg mercury/0.25 mL) was approved for use in individuals 6 months of age and older [Fluzone (Sanofi-Pasteur)]. Both of these formulations were packaged in single dose syringes or vials. Other influenza vaccines approved for use in older children and adults [Fluzone (Sanofi-Pasteur), Fluvirin (Novartis), Flulaval (GlaxoSmithKline)] contain 12.5 µg mercury/0.25 mL in multidose vials. Fluarix (GlaxoSmithKline), with <1 µg of mercury per 0.5 mL dose, has also been approved for use in adults. Beginning with the 2004–2005 influenza season, the Advisory Committee on Immunization Practices recommended routine annual use of IIV in 6–23 months old.

We were interested in searching VAERS to observe, in comparable ages of vaccine recipient, whether there were obvious differences in adverse events reported after administration of vaccine with and without thimerosal. Therefore, in addition to comparing the proportions of the most frequent adverse events in each group, we also compared proportions of adverse events that we hypothesized could possibly differ in the two groups. It is theoretically possible that non-preservative containing vaccines could confer a higher risk of infection (e.g., injection site abscess) compared with vaccines containing thimerosal. In contrast, delayed type hypersensitivity (DTH) to thimerosal has been documented by skin testing [2,8,9], but the association of skin test reactivity with local or systemic allergic reaction to thimerosal-containing vaccines has not been demonstrated [10]. The objectives of this exploratory study are to examine adverse event reports for influenza vaccines to see whether: (1) a higher proportion of reports were observed for post-vaccination infection after preservative-free vaccines (PFVs) than Preservative-Including Vaccines (PIVs) (2) a higher proportion of reports were observed for generalized rash or injection site reactions (ISR) after PIVs than PFVs?

Methods

We searched the United States Vaccine Adverse Event Reporting System (VAERS) for adverse event reports indicating possible infection or allergic reaction after PFVs and PIVs. Reports to VAERS that were reviewed for this analysis were those for infants <2 years of age received from 1 July 2004 to 4 January 2006. In recent years, VAERS has received 300–400 reports per influenza season after IIV in children <2 years of age.

VAERS is a passive surveillance system for adverse events following immunization (AEFI) jointly managed by the Centers for Disease Control and Prevention and the FDA.

Manufacturers identified the vaccine lot numbers that had thimerosal preservative, and those that were thimerosal-free. Vaccines for which the information provided to VAERS did not allow us to determine the thimerosal preservative status (e.g., no lot number reported, or a lot number that did not match the records from the manufacturers) were labeled “Preservative Unknown Vaccines” (PUVs). Coding terms were assigned to all reports based on the clinical content of the report using COSTART (Coding System for a Thesaurus of Adverse Reaction Terms); categorization of reports was based on coding terms. Each report may have more than one coding term. Coding terms indicating infection (either local or systemic), allergy, rash, or injection site reaction were sought. The adverse events labeled “Injection Site Reaction” included reports coded as hypersensitivity, mass, pain, or edema at injection site, injection site reaction, and/or those selected after review of reports coded as vasodilatation. The adverse events labeled “Infection” included reports coded as infection, bacterial infection, fungal infection, sepsis, abscess, and/or cellulitis (see discussion). The adverse events labeled “Rash” included reports coded as rash, urticaria, petechial rash, maculopapular rash, and/or skin ulcer (see discussion). Individual VAERS report review was performed for cases identified by ISR-related, infection-related, and rash-related coding terms. In some instances, reports were classified in more than one of the three categories.

Results

VAERS received 145, 175, and 216 reports, respectively, following vaccination with PFV, PIV, and PUV. Fever, rash, and urticaria were the most frequent adverse event coding terms assigned to reports in all three groups. The percentage of reports in the PFV, PIV, and PUV groups with rash-related coding terms was 41.4%, 40.6%, and 38.7%, respectively (see Fig. 1). The percentage in the PFV, PIV, and PUV groups with ISRs (see Fig. 1) was 15.9%, 15.4%, and 18.5%, respectively. The percentage in the PFV, PIV, and PUV groups with either local (e.g., cellulitis) or systemic infections was 8.3%, 8.6%, and 6.0%, respectively (see Fig. 1). Of note, none of the ISR reports in any category were coded as cellulitis or abscess. The top five COSTARTs in the “Other” category ($N=236$) in the Fig. 1 were fever (40.7%), convulsions (16.5%), agitation

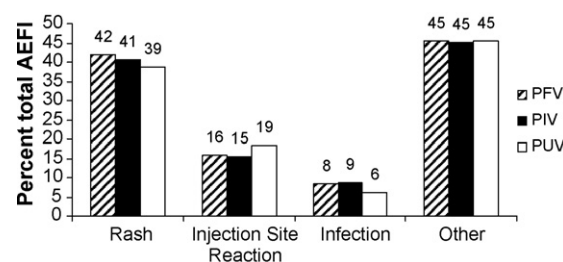


Figure 1 Adverse events by influenza vaccine preservative category. Comparative percent of adverse events following immunization (AEFI) with preservative-free vaccine (PFV, $N=145$), preservative-including vaccine (PIV, $N=175$), and preservative unknown vaccine (PUV, $N=216$). Adverse events do not necessarily represent confirmed diagnoses.

(11.0%), medical error (10.2%), and febrile seizure (8.9%). With the exception of the medical error reports, these reports were not individually reviewed, and each report may be coded with more than one COSTART. Medical error indicating age of administration lower than that indicated on the product label, without an associated AEFI, was reported relatively frequently (5% PFV, 29% PIV, and 22% PUV), but these reports were excluded from the analysis shown in the Fig. 1 since they were not associated with an adverse event.

Discussion

The acknowledged limitations of VAERS, including under-reporting, reporting bias, lack of a control group, lack of specificity in coding data, inadequate denominator data to calculate event rates and diagnostic uncertainty of events, might result in reporting patterns in VAERS that do not reflect the actual incidence of vaccine adverse events [10]. Because of the lack of availability of data on the number of people vaccinated in each group, we compared the proportion of reports of a particular AE in the PFV, the PIV, and the PUV groups to take into account the differing sizes of the three groups. There is precedent for use of such “surrogate denominators” in vaccine safety research [10]. Although similar proportions of AE types were observed across the three report groups, selective reporting of adverse events and variable completeness of the reporting itself [11], could result in misleading comparisons because relative proportions within VAERS do not always reflect relative rates. In addition, theoretically, if there were an increase in the total number of AEFIs within one of the three categories of reports because of an increased rate of those AEFIs, the proportion of an individual AEFI might stay the same despite the number of cases of that particular AEFI increasing. However, in this report, we know that the overall number of AEFIs was relatively similar between the three categories of reports. We have not used statistical tests of significance or confidence intervals in our analysis of these VAERS data because of the likely effect of the biases inherent to VAERS [10].

Lack of specificity in coding, may lead to imperfect groupings of reports. For example, the majority of the 14 reports of “skin ulcer”, were vesicular/crusted lesions after receiving both varicella and influenza vaccines, and other reports assigned this coding term were apparently assigned to describe local adverse events. Overall, it seemed more appropriate to put this group of reports with the “Rash” group rather than the “Injection Site Reaction” group. In addition, it is often difficult for clinicians to distinguish between an “injection site reaction” and “cellulitis”. Many reports in VAERS are coded as both. Here we made an artificial distinction between the two conditions based on what was written in the report, since we believe that the observer is in the best position of anyone to try to make that distinction. Another limitation of this study is the relatively high number of PUV reports. However, the PUV reports did not materially differ from the PFV and PIV reports with respect to the types of AEFI reported. In addition, although we did not see large differences in proportions of AEFI

reported between the PFV, PIV, and PUV groups as a whole, it is always possible that individual subgroups of the population could have idiosyncratic responses to vaccination, and this review would not necessarily pick up this type of information.

It would be optimal to have an accurate denominator, number of individuals in the U.S. in this age group that received IIV by preservative status. We do not have accurate age-specific data on the number of individuals that received PIV or PFV. Because available coverage data does not distinguish between the formulation of vaccine received, estimates of the number of infants that received each type of vaccine are not possible. (CDC, G. Wallace, A. Calugar, personal communication).

In summary, there were no substantial differences in the proportion of rash, ISR, and infection reports in the PIV, PFV and PUV reports in infants. We did not find evidence to support the theorized risks of either infection following PFV or hypersensitivity reactions following PIV.

Acknowledgments

Drs. Greg Wallace and Angela Calugar of the CDC National Center for Immunization and Respiratory Diseases.

References

- [1] Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics* 2001;107:1147–54.
- [2] Institute of Medicine (IOM). Thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC: National Academy Press; 2001.
- [3] Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal. *Environ Health Perspect* 2005; ehponline.org.
- [4] Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics* 2004;114:793–804.
- [5] Heron J, Golding J, The ALSPAC Study Team. Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the united kingdom does not support a causal association. *Pediatrics* 2004;114:577–83.
- [6] Notice to readers: thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR Morb Mortal Wkly Rep.* 1999;48:563–5.
- [7] Available at <http://www.fda.gov/cber/vaccine/thimerosal.htm> [accessed May 26, 2006].
- [8] Cox NH, Forsyth A. Thimerosal allergy and vaccination reactions. *Contact Dermatitis* 1988;18:229–33.
- [9] Reisman RE. Delayed hypersensitivity to merthiolate preservative. *J Allergy* 1969;43:245–8.
- [10] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23(4):287–94.
- [11] McMahon AW, Zinderman C, Ball R, Braun MM. Comparison of military and civilian reporting rates for smallpox vaccine adverse events. *Pharmacoepidemiol Drug Saf.* 2006 [Epub ahead of print].