The attenuated rubella virus vaccine: how public health agencies and the manufacturer thwarted post-release surveillance

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Abstract

Professor of Microbiology at University of Maryland, B. G. Young, Ph.D., became interested in conducting a follow-up study of adverse vaccine effects occurring in 10,000 individuals that initially received live attenuated rubella virus vaccine (HPV-77) in 1969.

Dr. Maurice R. Hilleman, Division of Virus and Cell Biology Research of Merck Institute of Therapeutic Research, published *Live Attenuated Rubella Virus Vaccine* in the 1969 Proceedings of the International Conference on Rubella Immunization held in Bethesda, Maryland at the National Institute of Health. In the summary section of that publication, he wrote, "Data file cards have been prepared on each of these children's name, address, and vaccination data so that they can be followed for their life-span for untoward effects should this be judged desirable. Adequate numbers of contact control subjects to exclude contagiousness have also been included in these studies."

The subject data that Merck was directed to maintain as part of licensure agreements, was requested for post-surveillance study, but never released. FDA's Bureau of Biologics stated, "There is no requirement [in licensure of *Merck, Sharpe and Dohme* for production and marketing of live rubella virus vaccine] for follow up of these named individuals."

Keywords: rubella vaccine, adverse vaccine effects, post-surveillance study

May 29, 1979: John Hoffman, a graduate student under Professor Young, wrote to Dr. Hilleman requesting information regarding follow up of these 10,000 subjects. Dr. Hilleman responded, "CDC, U.S.P.H.S., at Atlanta follows the vaccination program for side effects. Our subjects' cards are available as source material should any occasion arise when they are needed. They are on file at the Bureau of Biologics, FDA, Bethesda."

June 13, 1979: John Hoffman writes to Dr. William H. Foege, Center for Disease Control (Atlanta, GA) to obtain the patient cards.

June 26, 1979: John Hoffman receives a response from Hope E. Hopps, Assistant to the Director for Science (Bureau of Biologics), stating, "Dr. Hilleman was correct in indicating that the cards are on file here at the Bureau of Biologics and are 'available as source material should any occasion rise when they are needed.'" Mr. Hopps continues, "We have had no occasion to make use of the cards. If a problem presents itself at some time in the future, we have ready access to them."

July 2, 1979 A. David Brandling-Bennett, M.D., Chief Surveillance and Assessment Branch, Immunization Division (CDC, Atlanta, GA) writes, "The Center for Disease Control has no files on the subjects that have participated in rubella studies under the direction of Dr. Maurice Hilleman. I do not know what Dr. Hilleman was referring to in his response to your earlier letter and have no means of providing you the information that you desire."

May 17, 1980: John Chriss Hoffman appearing before the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in Washington, D.C., states, "Therefore, when Dr. Novitch, as Acting Commissioner of Food and Drugs, reports to this Commission that 'postmarketing data cannot provide sufficient information for estimating incidence of adverse [drug] reactions,' it is my belief that the reality of the situation would have been better described by saying that the Food and Drug Administration **does not** provide sufficient information for estimating incidence of adverse drug reactions."

May 21, 1980: John Hoffman writes to Mr. Morris B. Abram, Chairman President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, stating, "One of the adverse effects of rubella vaccination (during the period of 1969 to 1979) was failure of the rubella vaccine to confer long-lasting immunity, a fact of which the vaccine in most instances is not aware, with the result that a girl with a medical record indicating a history of rubella vaccination at a young age, reaches puberty and her child-bearing years with the understanding that she is immune to rubella infection. That this is not so, for a higher percentage of rubella vaccinees, is shown by information in a paper in the December 1979 issue of the *American Journal of Diseases of Children*. The author of the paper entitled *Rubella Reimmunization Now* suggests, because of the widespread failure of the rubella vaccine approved for use by the Food and Drug Administration in the 10-year period 1969-1979, that all prepubertal girls vaccinated in that period should be revaccinated."

June 30, 1980: Dr. Hilleman writes to Mr. Morris Abram stating in part, "My statement in the Journal of the American Medical Association in 1969 made it clear that these were to be a resource to be used 'should they be judged desirable.' And as Mr. Hoffman's statement also indicates, the Bureau has advised him that such a need has not arisen. We do want the record of the President's Commission to show that Merck fully carried

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out its promise to create a basic data file on rubella study subjects."

August 5, 1980: John Hoffman writes a letter to Mrs. Mishkin, Deputy Director for Policy Studies (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research), "… (1) How was it decided and by whom was it judged that use of 'the data file cards prepared in 1969 by Merck to identify 10,000 or more rubella vaccine recipients and control subjects', a resource to be used 'should they be judged desirable', is now an undesirable activity? (2) How was it decided and by whom was it decided that a need has not arisen for follow-up of the '10,000 or more rubella vaccine recipients and control subjects?'"

October 24, 1981: John Hoffman writes to the National Indian Brotherhood in Ottawa, Canada regarding the June 29-30, 1981 meeting of the U.S. Department of Health and Human Service's Food and Drug Administration Vaccines and Related Biological Products Advisory Committee presentations and discussions. Mr. Hoffman states, "To emphasize the concern arising from the involvement of FDA, CDC and Merck, Sharpe and Dohme in the introduction of hepatitis B vaccine, for demonstration purposes, in Alaskan Eskimos, I am enclosing copies of a presentation and correspondence that are formal records of the U.S. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. This presentation and correspondence came about as the result of … a serious failure of surveillance, for adverse effects, of 10,000 identified live rubella virus vaccine recipients and contact-control subjects over a ten year period following what we believe to be a promise by Dr. Hilleman in 1969 to the medical and scientific communities that the test and control subjects would be followed for their life-span for late untoward effects of vaccination. The reason for non-surveillance as stated by FDA's Bureau of Biologics was 'There is no requirement [in licensure of *Merck, Sharpe and Dohme* for production and marketing of live rubella virus vaccine] for follow up of these named individuals.'"

John Hoffman was so discouraged and disenchanted by the above events that he did not pursue scientific-medical research.

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