

A MULTICENTER, RANDOMIZED DOSE RESPONSE STUDY OF THE SAFETY,
CLINICAL & IMMUNE RESPONSES OF DRYVAX VACCINE ADMINISTERED
TO CHILDREN 2 TO 5 YEARS OF AGE

This study was previously discussed by Institutional Review Board #1 at the meeting on Tuesday, July 16, 2002.

The prior discussion focussed primarily on the adult data, risks and benefits to the individual participants, to contacts and to society .

Because of the serious and unusual nature of the concerns the members of Institutional Review Board #2 were asked to attend a joint meeting. (The investigator) was invited to attend in order to respond directly to the concerns.

There was a preliminary discussion of documents which were distributed to the Institutional Review Board prior to the meeting including the current recommendations of the Academy of Pediatrics and a recent article from "The Scientist". The history of smallpox vaccination including previous clinical practice and adverse events was discussed. The "Pediatric Rule" regarding the requirements for studying drugs in children was reviewed.

(The investigator) discussed the potential threat of bioterrorism. Information from federal sources, although classified, indicate that the threat is real. (The investigator) noted that there are vials of smallpox, the U.S. has it, the Russians have it. Do the terrorists have it, will they use it? Who knows? The government has made the decision to use the vaccine. The investigator does not have answers but it is assumed that the government does.

(The investigator) noted that there are several research questions. Because the vaccine is 30 years old it is not known how it will act. The vaccine will be diluted (1:5 in the present study). The number of punctures will be different than the previous studies in adults.

Since a new vaccine is in the process of being developed. (The investigator) was asked why not wait? (The investigator) noted that the federal government says we should move forward with the present vaccine. In case of a terrorist attack police, firemen and contacts will be vaccinated immediately.

A semi-permeable occlusive bandage will be used to prevent spread of the virus. This was specifically contraindicated 30 years ago. It was noted that this is a semi-permeable bandage which was not available 30 years ago.

There was a discussion of the data from the recent adult studies. (The investigator) noted that there were more satellite lesions with the diluted vaccine.

It was noted repeatedly that the risks to contacts are different than 30 year ago because of HIV, patients on chemotherapy, patients on steroid therapy, etc.

who has had experience working with vaccinia virus in laboratory animals described the experiences with smallpox vaccination in laboratory personnel. Dr. who had vast experience with smallpox vaccination in children more than 30 year ago discussed the lack of significant adverse events and the lack of spread to contacts at that time. As noted most, if not all, contacts had previously been vaccinated.

There were questions related to isolating children for 30 days. (The investigator) noted that it is important that they keep the bandage on. inquired about taking children to the grocery store, mall? (The investigator) responded, "that as long as they keep the bandage on it is fine. Some responsibility will have to be taken by the parents". Dr. asked, "Why can't you use an isolation place - like a safe house, camp, etc.?" (The investigator) responded that this is not realistic, just keep the site covered. Dr. noted even a responsible parent would have difficulty keeping the site covered. How difficult is it to get the covering off? Dr. noted that similar bandages are used on Hematology/Oncology patients and that they are really hard to remove.

Dr. asked what would happen if the virus spreads to contacts. (The investigator) responded that there would be an isolated skin lesion. It is emphasized that this is not smallpox virus. This is vaccinia virus. Dr. suggested that the comprehension quiz should be more comprehensive in order to address concerns regarding transmission and the risks to contacts.

commented that whoever is recruiting subjects needs to be sensitive regarding the potential subjects. Are the subjects aware and appropriately concerned about the risk to others? Will they behave responsibly? (The investigator) added, "we are concerned about that too". Dr. suggested that there may need to be some method to sort out those families who may not be responsible. There may be a need for someone with expertise in that area to help in the recruitment process.

(The investigator) suggested that the risks may be overplayed. The consent form can be frightening because of the list of all known possible side effects some of which are severe but exceedingly unlikely.

(The investigator) suggested that there could be a direct benefit with more than minimal risk. Dr. noted that there would only be a direct benefit for the participants in the case of a terrorist attack.

Dr. inquired about the scientific merit. From the adult data and from the investigator's experience is there any reason to suspect that the stored full strength will not be effective and is there any reason to think the 1:5 dilution will not work?

(The investigator) noted that the full strength vaccine should work, but noted that it is 30 years old. Also there is a difference in the dose administered between 5 punctures (which will be used in children) and 15 punctures (that has been used in the adult studies).

Questions were asked regarding the sample size. The total study will involve 40 subjects divided into 2 groups of 20 each. (The investigator) referred to the table of probabilities in the statistics section of the multicenter protocol which was designed with statisticians. If the take rate is less than 50% the 1:5 dose can be eliminated. This is a pilot study. It will not provide final answers.

(The investigator) noted that these discussions are going on at high levels. It was emphasized that at this time there is not enough vaccine to be able to vaccinate everybody.

Dr. questioned the value of the study. "What information will be obtained by just giving it to children?" (The investigator) replied, "that if there is an outbreak in a month who would get it?"

Dr. replied, "It would be distributed on the basis of supply and demand. If there is enough everyone would receive it undiluted. If not, it would be administered in a 1:5 dilution."

(The investigator) responded that there is no choice. "If the 1:5 dilution is effective it would be used and as a result more people could be vaccinated."

Dr. responded that this would not be done unless there was not enough vaccine for everyone.

(The investigator) stated that is the idea, to have enough vaccine for everyone. He also added that the study could be done in a couple of months and something would be known about the efficacy and safety of the 1:5 dilution in children.

There were questions regarding possible markers to identify subjects who should not receive the vaccine. (The investigator) responded that this is being considered for the next study. Exclusion based on history of eczema is interesting because it is assumed that in patients with active disease who have damaged skin, the lesions would spread because this is not an intact barrier. It turns out that even patients with a history of eczema are at risk.

Dr. inquired about the dose that would be administered.

(The investigator) repeated the discussion regarding dose (5 pricks vs. 15 pricks), different dose for children, safety issues, these are a primary concern. They will learn about side effects. He also added that in the 1970's physician did what they wanted, the rule was somewhere between 3 and 15 pricks.

Dr. _____ summarized the discussion stating that the primary objective is efficacy. The dose is different for adults. If this study shows that 1:5 doesn't work then it will influence the dose given to many people. There are also side effects that will influence what is done. These are not known now. It is not known what happens to a child's skin when it is covered.

(The investigator) responded that children are not small adults and that this study will influence how children are vaccinated in the future.

_____ questioned if it is known whether the vaccine that was administered over 30 years ago still has an effect. (The investigator) noted that this is not known, there may be some residual immunity.

(The investigator) responded that no blood tests will be done to determine levels of protection. This will be included in future studies.

Dr. _____ asked if subjects will sign all three consent forms up front.

(The investigator) responded that the consent forms for treatment of systemic disease will be available but will be used only if necessary. There will be an extensive information sheet that will be given to parents.

(The investigator) left the meeting at this point.

There was a discussion regarding liability issues.

Dr. _____ raised questions regarding the liability of the Institutional Review Board and the members of the Institutional Review Board.

Dr. _____ noted that the government has no liability and that the local Institutional Review Board and investigators, are liable.

The FDA is only concerned with safety. Dr. _____ suggested that this study may come under the vaccine protection act.

Dr. _____ noted that this study is an efficacy study and that there is value in knowing the appropriate dose for children.

Dr. _____ noted that this Institutional Review Board has historically not included the benefit to society, but it may be appropriate in this case.

Dr. requested that even if there was full supply, there might still be a rationale for testing in children because of dose. In six months time we may have another vaccine and there may be enough for everybody but we still need to know the dose for children.

Dr. responded that it is hard to justify not acting in a reasonable manner because something could happen today, tomorrow, or ever.

Dr. questioned if we do the study and there is a 50% take at 1:5 and three months from now there is an outbreak, and there is not enough vaccine what will be done then?

Dr. noted that this is more reason to understand what is and what isn't reasonably possible.

Dr. expressed clarification regarding the comparisons which have been made to other vaccines such as diphtheria. In other situations the vaccine was perceived to be protective. In those situations there would be direct benefit to the patient. In this situation it may be hard to see the direct benefit. Dr. agreed and added that the other situations are seen as protective. At the present there are no cases of smallpox in the world.

Dr. noted that from that perspective it is more of direct benefit compared to others. Smallpox spreads like wildfire. In that case everyone will get diluted vaccine.

questioned how patients will be enrolled and how can they be sure that people understand the risks to other people. supported the suggestion that someone on the team who understands the risks should be included in the consent process because of concerns that people may not understand the potential risks related to spread to someone else.

Dr. questioned if the Institutional Review Board should recommend another person to witness the consent process.

Dr. suggested a more formal screening process. It is unknown who would be volunteering or how rational the people may be. There are significant psychological issues. Having somebody just witness the consent process will not tell you a lot. You have to make sure you are dealing with someone who will make a rational choice and also be sure that you are dealing with a family who can control the possible exposure of contacts. If you are dealing with a family that deals in chaos this may not be possible.

Dr. agreed, but expressed his concerns we are getting caught up in the smallpox thing. He feels that the risk is much less than a child getting into a bottle of study medicine sent home for a blood pressure study. He noted that if there is a need to find the "right" families, then the results will not apply to the general population.

Dr. stressed the concern regarding children vs. adults and how they will be dosed. The outcome of this study will either lead to a bigger study or influence the decision about how people are going to be dosed. The risks are relatively minor compared to the value of the study. He noted two things - a difficulty to measure risk to society and a difficulty to measure benefit to society. He added that if there is an outbreak the information from this study or the extension of this study will be used to determine the size of the population for a possible ring vaccination program. This may involve adults and may involve families of adults (including children).

indicated that any motion should include a statement regarding the comprehension quiz.

Dr. indicated that we need to vote on a motion. If it is approved it can go forward as is. If not, we may then want to vote on another motion.

Dr. questioned whether both IRB #1 and #2 should vote on this study. He questioned why are we creating a new set of rules for a specific protocol. This establishes a precedent and is not a good idea.

(The Chairman) responded that including both IRBs was suggested because of the broad institutional and societal concerns and the importance of this study.

Dr. questioned that. If we make a special situation for this study what are the implications for other studies (i.e. gene therapy).

Dr. discussed a motion to approve the study with recommendations to change the protocol to include more comprehensive screening of parents and that both parents should sign the consent form and with addition to the comprehension quiz regarding risk to contacts.

The members of Institutional Review Board #2 departed. Dr. remained as a non-voting member.

It was noted that a quorum of IRB #1 remained including a non-scientist.

The study was determined to be more than minimal risk with potential direct benefit.

Subject assent is not required because of the age of the subjects (2-5 years of age).

The permission of both parents is required for this study.

IRB Meeting
July 30, 2002

After the guests left Dr. made a motion to approve the study with additional screening as discussed above, the approval of both parents and the improved comprehension quiz. seconded the motion and it was approved.

Total = 9; Vote: For-6, Opposed-2 (Dr. and),

Abstained-0. The Chairman did not vote. One community, non-scientific member was present for the vote.

The study was approved for a period of one year.