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MULTIPLE ANTIGEN ADMINISTRATION

Simultaneous Administration of Several Vaccine Agents as Mixed Preparations and as Separate Inoculations

by

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INTRODUCTION

The simultaneous administration of several agents as part of a smallpox vaccination campaign is highly attractive for several reasons. In most countries where smallpox is still endemic, there are other immunizable disease problems which cause greater morbidity and mortality than smallpox. The most difficult aspect of a mass campaign is the gathering of people physically together to receive any immunization. To let the opportunity pass without administering as many immunizing agents as possible seems a senseless waste. Finally, by administering several immunizing agents simultaneously during the course of a mobile campaign, one may bring to bear on the population effective control of immunizable diseases in the absence of the developed health infrastructure necessary to the prophylactic practices common in the western world.

It is sensible to do simultaneous multiple antigen administration providing it can be shown that such combinations are (a) safe and (b) effective. When this is assured, the logistical and economic considerations would dictate that multiple antigen administration be utilized wherever possible.

A number of antigens must be considered as candidates for simultaneous administration with smallpox vaccine. Such antigens in some instances have been physically combined with smallpox vaccine producing a mixed vaccine which is administered with a single injection at a single site. More frequently, smallpox vaccination by the scarification or multiple pressure method has been accompanied by the administration of other agents simultaneously but in separate sites and by different routes. This is referred to as "simultaneous multiple antigen administration" but does not imply a physical mixing of the vaccines.

Of the available antigens, there are several which would appear attractive for simultaneous administration in most endemic areas by virtue of the chronic endemicity, the severity and the frequency of such diseases in endemic areas; diphtheria-pertussis-tetanus antigens, polio, yellow fever, measles and BCG vaccines.

In this paper, the available information on these various combinations both as "mixed" vaccines and as "simultaneously administered multiple antigens" will be examined with regard both to safety and efficacy.

SMALLPOX VACCINE COMBINED WITH KILLED ANTIGENS

There is no evidence of an increased risk or a decrease in the efficacy attending the simultaneous use of smallpox vaccination with the killed antigens such as diphtheria, pertussis, and tetanus and/or typhoid. The route and sites of administration are necessarily different. The combination at present is an accepted part of paediatric practice in the western world.

SMALLPOX VACCINE COMBINED WITH KILLED AND LIVE AGENTS

Winter and others [1] administered smallpox (by multiple pressure) simultaneously with DPT (by subcutaneous inoculation) and live oral polio vaccine to 22 children. No measurement of the pertussis efficacy was made. All 22 showed evidence of DT and oral polio Types II and III seroconversion. Twenty-one of the twenty-two deyeloped smallpox pustules and 21 of the 22 had Type I polio seroconversion. There was no evidence for diminished efficacy accompanying this schedule of combined administration. The same schedule was subsequently applied to 882 infants without any apparent increase in morbidity.

There appears no technical reason to withhold such a combination of agents.

SMALLPOX VACCINE COMBINED WITH OTHER LIVE VIRUS AGENTS

The combined use of smallpox, measles, and yellow fever vaccines has attracted great attention particularly in Africa where all three diseases threaten. The antigens have been administered both as single injections of mixed vaccines, and as simultaneous but separate injections of the individual components. Success with these combinations has been variable.

1. Smallpox Vaccine Combined with Yellow Fever Vaccine

Of the various live-live combinations, this one has met with most problems both as regards safety and efficacy. Both agents (especially the Dakar yellow fever virus) can cause central nervous system complications in a proportion of recipients. The high incidence of central nervous system complications (0.5 per 1,000) following the simultaneous administration of Dakar yellow fever and smallpox vaccine by scarification prompted Combescot de Marsaguet and Thomas to advise against this combination.[2]

While the simultaneous administration of 17D yellow fever vaccine and smallpox has not caused significant safety problems, there have been difficulties with efficacy. Dick and Horgan[3] in 1952 showed that 17D yellow fever vaccine and smallpox vaccine mixed and administered as a single inoculation led to satisfactory results with the smallpox component; however, only two-thirds of the subjects demonstrated yellow fever seroconversion. In contrast, when the two agents were administered simultaneously but seperately (yellow fever subcutaneously and smallpox by scarification) 100 per cent of the subjects showed seroconversion to the yellow fever component. Meers[4] confirmed this in 1959 showing that only 64 per cent of non-immunes inoculated by mixed 17D yellow fever and smallpox vaccine by scarification showed evidence of seroconversion to yellow fever. Meyer[5], in using a measles-yellow fever-smallpox mixture, found a reduction to 85 per cent of the yellow fever seroconversion rate in Voltan children.

The available evidence suggests that the smallpox-yellow fever combination is effective when the two agents are not mixed together as a common injectable. When mixed, there is a reduction in the efficacy of the yellow fever component, presumably due to interference. Limited data cast doubt on the safety of administering Dakar strain yellow fever vaccine and smallpox vaccine simultaneously.

2. Smallpox vaccine combined with measles vaccine

Little information is available on this combination. Table I summarizes the frequency of febrile responses to measles-smallpox (and measles-smallpox-yellow fever) combinations.

TABLE I

% Temp. ≥ 103°F. *
(Temperatures ≥ 104°F. shown in parentheses)

Author	Edmon. B.-Spox -Y.F.	Edmon. B-Spox	Beckenham-Spox	Edmon. B.	Spox	Y.Fever
Meyer [1]	20(6)	23(2)		20(4)	11(1)	12(4)
Togo [2] (CDC)		39(24)		30(6)	19(10)	
Hendrickse [3]		29	10		9	
Weibel [4]		28			0	

* Approximately 100 children were tested in each vaccine group with the exception of the fourth study (see footnote).

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1. Meyer, et al Bull. WHO 30 : 783, 1964

   Studies were carried out in Upper Volta; vaccines were mixed for purposes of administration; proportion with high temperatures recorded in table are shown for ≥ 39° C (102.2° F.) and, in parentheses, for temperatures ≥ 40° C. (104° F.).

2. Budd, et al (CDC studies)

   Vaccines were administered simultaneously but in opposite arms.

3. Hendrickse (Personal communication)

   Studies were conducted in Nigeria; vaccines were administered simultaneously but in opposite arms.

4. Weibel, et al (Paediatrics 37 : 913, 1966)

   Studies were conducted in Pennsylvania; vaccines were mixed and administered; two studies were done in the same population group; children were apparently studied in an incidental manner. In one group 5 of 12 children developed fever 103° F.; in the other group o of 6.

In Hendrickse's study[6] and in the CDC-Togo study[7], the febrile response following administration of measles and smallpox vaccines were notably greater than when measles vaccine or smallpox vaccine was given alone.

During 1965, CDC and Panamanian health authorities evaluated 5,261 children to whom Edmonston B measles vaccine and smallpox vaccines were simultaneously but separately administered.[8] From the 5,261, 4,250 were estimated to be non-immune to both measles and smallpox. Complications which occurred during the fourteen-day post vaccinal period included eleven convulsive episodes, six cases of generalized vaccinia and eleven cases of auto-inoculation vaccinia. One death occurred which was felt unrelated to vaccination but incomplete documentation precluded a definite conclusion. On the basis of the rate for generalized vaccinia in the United States reported by Neff[9] (20.8 cases per million primary vaccinations), the six cases which occurred in the Panama study would seem to be an increased incidence of this complication. Since data are not available on the usual incidence of generalized vaccinia in Panama, this finding is difficult to interpret.

In 1965-66, mixed measles-smallpox vaccine was given to 18,000 children in Upper Volta in a study sponsored by that Government and the Merck Institute[10]. The vaccine was given by jet gun in a dose of 0.5 ml. By the use of an adapted nozzle, some of the mixture was felt to be injected intradermally. It was reported that the smallpox component elicited "positive reactions (primary, vaccinoid, immune)" in 98 per cent (conventional WHO designations are not given). There was no indication of interference between the vaccines as measured by antibody or dermal response. The investigators also state "the mixture did not cause serious clinical reactions or increase in febrile reactions above that expected for either vaccine given alone". The mechanism for follow up of febrile and other reactions was basically one of passive surveillance.[11] Mothers were asked to return their children to the clinic at specified times for an evaluation. Temperatures were taken only if the child appeared clinically feverish, etc. It is thus difficult to interpret with assurance the findings presented on the apparent safety of the procedure.

3. Smallpox Vaccine combined with measles and Yellow Fever vaccines.

This combination has been evaluated by Meyer [5] and the complete assessment of the combination is limited to approximately 100 children. The study demonstrated no differences in the frequency of febrile responses among those given measles, measles-smallpox, and measles-smallpox-yellow fever vaccines. The proportion showing significant febrile responses is somewhat low contrasted to most other studies of Edmonston B, a finding for which no explanation is given. Seroconversion for the yellow fever component was reduced where yellow fever was mixed with measles and smallpox. This is consistent with findings reported above. Meyer also observed that the combination of smallpox with measles, and with measles and yellow fever, while not reducing the rate of seroconversion to vaccinia, was accompanied by a reduction in the mean post vaccinate vaccinia neutralizing antibody in recipients of the mixed vaccines. This was most marked with the smallpox-measles-yellow fever mixture.

On the basis of these available data, administration of the three agents separately but simultaneously appears neither unsafe nor diminished in efficacy. Mixing of the three, however, results in reduction of the efficacy of the yellow fever component and perhaps the smallpox component as well. There is a suggestion that the measles-smallpox combination in Panama led to an increase in the occurrence of generalized vaccinia although the data are insufficient for a confident conclusion.

SMALLPOX - BCG

BCG is an immunizing agent commonly administered to children in a number of tropical areas. The simultaneous administration of this in a smallpox vaccination campaign is of interest to many countries and of intense interest to African health workers. There have been three reports published regarding simultaneous vaccination with BCG and smallpox vaccine. [12,13,14]. Moddy and Cheng [12] reported on concurrent BCG and smallpox vaccination (both by multiple pressure technique) in 300 000 newborn infants in Hong-Kong. No complications occurred. They concluded that BCG had no effect on the primary take rate while the Mantoux conversion rate and BCG reactions compared favourably with results others have reported when BCG was given alone.

A second study[13] was conducted in Taiwan in 696 newborns divided into three equally sized groups and vaccinated by one of the following schedules:

1. Simultaneous vaccination with smallpox and BCG vaccines
2. BCG only
3. Smallpox vaccine only.

Smallpox vaccination was done by the double scratch techniques using liquid lymph while BCG was administered by intradermal injection with needle and syringe. The vaccines were given in different arms. No differences were observed with respect to smallpox vaccination between the group given smallpox vaccine and BCG simultaneously and the group given smallpox vaccine alone. Primary take rates, the frequency of distribution and the size of vaccination reactions and the response to revaccination at twelve weeks were the same in each group. Tuberculin tests at twelve weeks gave a normal distribution; tuberculin reaction sizes showed a mean of 11.94 millimeters for the "simultaneous" group and a mean of 12.19 for the "BCG only" group. In the "smallpox only" group, all tuberculin reactions were less than 9 millimeters, the majority being 0-3 millimeters. There were no observed BCG complications. There were five mild smallpox complications, three in the simultaneous group and two in the smallpox only group. All recovered without difficulty. The author concluded that simultaneous vaccination with BCG and smallpox vaccine was a safe and effective procedure.

A recent study explores the possible interaction of primary BCG vaccination and smallpox revaccination in 1,099 Burmese children. Revaccination take rates among negative tuberculin reactors administered BCG were not different from those among similar subjects who did not receive BCG. Similarly, there was no differences in the revaccination take rates between tuberculin positive and tuberculin negative children. The authors concluded on the basis of their studies that there was no apparent interaction between BCG primary vaccination and smallpox revaccination.

All the available data on the simultaneous administration of BCG and smallpox vaccine indicate that simultaneous administration of these two agents can be done without loss of safety or effectiveness. There are no studies available on the administration of BCG and vaccinia virus as a mixed vaccine.

COMBINATION OF SMALLPOX, MEASLES, YELLOW FEVER AND BCG VACCINES

While no data have been published on this combination, simultaneous administration of these antigens is now being practised in some parts of Africa. Since natural infection of measles may exacerbate tuberculosis and since the administration of measles vaccine diminishes the tuberculin sensitivity,[15] there is reason to believe that a measles-BCG, simultaneous administration might interact in an unfavourable manner. This combination can therefore be recommended at this time only on an experimental basis. Should careful observations justify its use, the simultaneous administration of these four antigens would have great logistical attractiveness.

GENERAL SUMMARY

The present state of knowledge would indicate that :

1. Smallpox can be administered simultaneously with DPT and oral polio vaccine without diminution in effectiveness or safety.
2. The simultaneous administration of two or more of the live virus vaccines, smallpox, measles, and yellow fever, results in :
   a.) A more pronounced febrile response than does the administration of a single agent. Although the simultaneous administration of the smallpox and measles vaccine has been tested in reasonably large numbers of susceptibles, only 100 children (Meyer study) have been evaluated with respect to simultaneous administration of all three.
   b.) Given at separate sites, there does not appear to be a decrease in the efficacy of any of the components.
   c.) When given as a mixture, there may be a decrease in the efficacy of the yellow fever component.

3. The available evidence on the combination of BCG and smallpox vaccine indicates that simultaneous administration of these two antigens is both safe and effective.

4. There are no data available assessing the simultaneous administration of measles, smallpox, yellow fever and BCG although this combination is being practised. This procedure cannot be recommended until there is clearcut evidence for lack of interaction between the measles and BCG components.

No studies are yet available to assess the maximum number of antigens which may be simultaneously administered with both safety and efficacy. However, there is no evidence at hand now to indicate that smallpox, polio, DPT, yellow fever and measles vaccines cannot be safely and efficaciously administered providing the yellow fever component is separately administered. Should the BCG-measles combination prove to be safe and efficacious, it is clearly possible that all the agents mentioned above could be administered simultaneously. The economic and logistic ramifications of such a practice in the developing countries are immense.

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