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SIMULTANEOUS ADMINISTRATION OF SEVERAL ANTIGENS

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INTRODUCTION

The simultaneous administration of several antigens in an immunization programme is obviously more economical than arranging for the administration of each on a separate occasion. Provided that a combination of various antigens can be shown to be (a) safe and (b) effective, the logistical and economic considerations would dictate that multiple antigens be administered wherever possible.

A number of antigens may be considered as candidates for simultaneous administration with smallpox vaccine, including diphtheria-pertussis-tetanus antigens, polio, yellow fever, measles, BCG and typhoid vaccines. Such antigens in some studies have been physically combined with smallpox vaccine and administered with a single injection at a single site. (Referred to as combined or mixed vaccines.) More frequently, smallpox vaccination has been accompanied by the simultaneous administration of other antigens but at 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.

In this paper, information on 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 attendant upon the simultaneous use of smallpox vaccine and killed antigens such as diphtheria, pertussis and tetanus, and/or typhoid. The route and sites of administration are necessarily different. Simultaneous administration of these antigens is accepted paediatric practice.

SMALLPOX VACCINE COMBINED WITH KILLED AND LIVE AGENTS

Winter et al.[1] administered smallpox (by multiple pressure) simultaneously with DPT (by subcutaneous inoculation) and live oral polio vaccine to 22 children. All 22 showed good seroconversion responses to diphtheria and tetanus toxoids and oral polio vaccine types II and III. Twenty-one of the 22 had primary smallpox vaccination takes and 21 of the 22 showed seroconversion to type I polio vaccine virus. (There was no measurement of the efficacy of pertussis.) There was no evidence of diminished efficacy or adverse reactions accompanying this schedule.

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 are a major threat. 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 combinations of live antigens, this one has met with the most problems, both as regards safety and efficacy. Both agents (especially the Dakar mouse brain yellow fever vaccine) can cause central nervous system complications in a proportion of recipients. While the original studies of efficacy showed high seroconversion rates when a combined vaccine was used (Dakar strain yellow fever, vaccine virus),[2] the high incidence of central nervous system complications in one study prompted Combescot De Marsaguet & Thomas to advise against this combination.[3]

The administration of 17D yellow fever vaccine and smallpox as a mixed vaccine has not caused significant adverse reactions, although there have been difficulties with efficacy. Dick & Horgan[4] in 1952 showed that 17D yellow fever vaccine and smallpox vaccine mixed and administered as a single inoculation led to satisfactory results so far as vaccinia was concerned; however, only two-thirds of the subjects demonstrated yellow fever seroconversion. Meers[5] confirmed this in 1959 showing that only 64 per cent. of non-immunes inoculated by mixed 17D yellow fever and smallpox vaccines by scarification showed evidence of seroconversion to yellow fever. Meyer,[6] in using a measles-yellow fever-smallpox mixture, found that only 85 per cent. showed seroconversions to yellow fever.

In contrast, when the two agents were administered simultaneously but at separate sites by Dick & Horgan (yellow fever subcutaneously and smallpox by scarification), all subjects showed seroconversion to the yellow fever component and a satisfactory response to smallpox vaccine. Studies by Ruben et al.[7] in Northern Nigeria confirm the efficacy of simultaneous administration of smallpox and 17D yellow fever vaccines.

The available evidence thus suggests that the smallpox and 17D yellow fever vaccines are effective when administered at separate sites but, when mixed, there is a reduction in the efficacy of the yellow fever vaccine.

2. Smallpox vaccine combined with measles vaccine

The debrile responses noted by Meyer following simultaneous administration of measles and smallpox vaccines were not notably greater than when measles vaccine was given alone.[6]

Studies indicate smallpox and measles vaccines can be given combined or as simultaneous injections without increased complications or decreased efficacy.[8,9,10]

3. Smallpox vaccine combined with measles and yellow fever vaccines

This combination has been evaluated by Meyer[6] who administered the vaccines as a mixture 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. For no apparent reason, the proportion of children showing significant febrile responses was somewhat lower than in most other studies in which the Edmonston B strain of measles vaccine was used. The frequency of seroconversion to yellow fever was reduced as noted above, when yellow fever was mixed with the measles and smallpox vaccines. 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 geometric mean vaccinia neutralizing antibody in recipients of the mixed vaccines. This was most marked with the smallpox-measles-yellow fever mixture.

Ruben administered smallpox, measles and yellow fever vaccines simultaneously but at separate sites to 90 children. Seroconversions to yellow fever vaccine were observed in 97 per cent., measles seroconversions in 90 per cent. and primary smallpox vaccination responses were present in 98 per cent.

On the basis of these available data, administration of the three agents separately but simultaneously appears both safe and efficacious. Mixing of the three, however, results in reduction of the efficacy of the yellow fever component and perhaps the smallpox component as well.

4. Combination of smallpox, measles, mumps and trivalent polio vaccines

Studies in Baltimore, Maryland, United States of America, on the simultaneous administration of measles, mumps and smallpox vaccines have demonstrated no problems in regard to safety or efficacy. In the same studies, measles, smallpox, mumps and trivalent polio vaccines were administered simultaneously, also with no evidence of difficulties in regard to safety or efficacy.[11]

SMALLPOX-BCG

Moody & 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 with BCG given alone.

A second study[13] conducted in Taiwan showed that simultaneously administered smallpox and BCG vaccine was as efficacious as either administered separately.

All 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.

OTHER COMBINATIONS

Measles, mumps and rubella vaccines have been recently tested as combined vaccines and have also been administered simultaneously at different locations.[14,15,16] Either form of administration appears safe and efficacious.

Measles and BCG vaccines have been given simultaneously for several years in West and Central Africa. Concern over the possibility of interference has been expressed because of previous observations that measles vaccine can alter the tuberculin skin test. Dutertre found no interference when the two antigens were administered simultaneously.[17] Rey, with a mixed vaccine, reports 95 per cent. seroconversion with measles vaccine alone and 90 per cent. seroconversions to measles with the mixed vaccines.[18]

GENERAL SUMMARY

The present state of knowledge would indicate that:

1. Smallpox vaccine can be administered simultaneously with DPT and oral polio vaccine with full efficacy and without an increase in adverse reactions.

2. Smallpox vaccine can be safely and effectively administered simultaneously with, or in combination with, measles vaccine.

3. The simultaneous administration of smallpox, measles and yellow fever vaccines results in:

(a) No decrease in the efficacy of any of the components if given separately.

(b) When given as a mixture, there may be a decrease in the efficacy of the yellow fever component.

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

5. The simultaneous use of smallpox, measles and mumps vaccines appears effective and the addition of polio vaccines to this combination has been shown to be effective in one study.

6. Measles, mumps and rubella vaccines can be administered separately or in combination.

7. Preliminary data on the simultaneous use of measles vaccine and BCG shows no evidence of interference between the two vaccines.

A summary of pertinent studies is presented in Appendix A.

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APPENDIX A

Vaccine Combinations	Combined	Simultaneous Separate	Conversion Rate Multiple	Conversion Rate Control	Reference
Smallpox Yellow Fever	X X		NR 98	NR 99	Peltier, M. Am. J. Pub. Hlth., (1947) 37:1026-1032
Smallpox Yellow Fever		X X	100 100	NR NR	Dick, G.W.A. and Horgan, E.S. Am. J. Hyg., 1952, 50:376-383
Smallpox Yellow Fever	X X		100 67	NR NR	
Smallpox Measles	X X		98 100		Kalabus, F., et al. Am. J. Epid., 1967, 86:95-111
Smallpox Measles - Attenuated		X X	97 96	100 96	Budd, M., et al. Am. J. Pub. Hlth, 1967, 57:80-86
Smallpox Measles - Attenuated		X X	97 93	100 NR	Sherman, et al. Brit. Med. J., 1967, 2:672-676
Smallpox Measles - Further Attenuated		X X	97 87	100 NR	
Smallpox Measles - Further Attenuated	X X		98 99		Weibel, R.E., et al. Ped., 1969, 43:567-572
Smallpox Measles - Further Attenuated	X X		100 98		Villarejos, V.M. Am. J. Epid., 1971, 93:384-391
Smallpox Measles - Attenuated Yellow Fever	X X X		100 98 85	100 97 97	Meyer, H.M., et al. Bull. Wld. Hlth. Orgn. (1964) 30:783-794
Smallpox Measles - Further Attenuated Yellow Fever - 17D		X X X	98 83 97		Ruben, F.L., et al., to be published.
Smallpox Measles Yellow Fever Diphtheria Pertussis Tetanus		X X X X X X	97 68 95 87 100 70	 89 98 80	

Vaccine Combinations	Combined	Simultaneous Separate	Conversion Rate Multiple	Conversion Rate Control	Reference
Measles and Gamma Globulin (Attenuated)		X	95	NR	Froeschle, M.D., and Casey, H. J. Ped. (1964), 30:783-794
Polio		X	95	NR	
Mumps - Leningrad 3	X		95	98	
Rubella-Leningrad 8	X		94	96	
Mumps	X		89	98	Smorodintsev, A.A., et al.
Measles-Leningrad 16	X		89	97	Bull. Wld. Hlth. Orgn., (1970)
Measles	X		91	97	42:283-289
Rubella	X		96	96	
Measles	X		91	97	
Mumps	X		92	98	
Rubella	X		91	96	
Measles	X		100	100	
Mumps	X		93	100	Buynak, E.B., et al.
Rubella	X		100	100	JAMA, 1969, 207:2259-2262
Measles	X		100	NR	Krugman, S., et al.
Mumps	X		100	NR	Am. J. Dis. Child. (1971)
Rubella	X		98	NR	121:380-388
Measles		X	98	94	
Mumps		X	86	93	Karchmer, A.W., et al.
Poliomyelitis		X	71-90		121:382-388
Smallpox		X	98	95	Am. J. Dis. Child. (1971)