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Antibody Response in Mice Inoculated with Monovalent or Trivalent Foot-and-mouth Disease Vaccines

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With 7 tables

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In a previous communication (2), a new potency test for foot-and-mouth disease (FMD) vaccines in adult mice was described based on the observation (1) that mixtures of serum from vaccinated mice and type-specific antigen bind complement (C′), the amount of C′ fixed being proportional to the potency of the murine serum (2). Monovalent FRENKEL-type vaccines of different potency in cattle could be distinguished by a complement-consumption test (CCT) with serum pools from vaccinated mice, a modified direct complement-fixation test in which C′ left free, rather than C′ fixed, is measured in mixtures with mouse immune serum (MIS) and antigen (Ag) subjected to cold fixation (2).

The present paper deals with the antibody response, as measured by CCT, in individual mice treated with monovalent and trivalent vaccines, respectively. It shows that monovalent vaccines stimulated the formation of complement-fixing antibodies less than trivalent vaccine containing the same antigenic components in smaller quantities. A further subject is the number of mice to be used in potency tests of monovalent and trivalent FMD vaccines.

Materials and Methods

Monovalent vaccines tested, modes of vaccination and serum collection as well as techniques used in CCT according to the constant serum and the serum dilution methods were described in detail previously (2).

Trivalent vaccines, vaccination and bleeding

Trivalent vaccine I was prepared by mixing equal quantities of monovalent FRENKEL-type vaccines O-8172, A-8216 and C-8327 (IFFA, Lyon). The cattle dose prescribed for each of these vaccines was 1.6 ml. For comparison we tested trivalent vaccine II, a foreign commercial product also prepared according to the FRENKEL method. We have no information about this vaccine except that it contained antigens of Types O, A and C. The dose recommended for cattle was 15 ml.

Based on the dosage for cattle, trivalent vaccine I was given subcutaneously (sc) in doses of 0.25 and 0.5 ml. to groups of 24 mice (7—8 week-old females of the NMRI strain). Two groups of 24 mice each received trivalent vaccine II in doses of 0.75 and 1.5 ml., respectively. The animals were bled on day 33 post vaccination (pv), keeping samples from individual mice separate. The interval between vaccination and bleeding was the same with monovalent and trivalent vaccines (2). Pools were made by withdrawing equal small amounts from individual samples.

CCT

In CCT according to the constant serum and serum dilution methods (2), sera from mice treated with trivalent vaccine were tested against antigens of Types O, A and C using the same technique as for monovalent mouse immune serums (MIS).

Results

Mode of reaction of serum pools from mice treated with trivalent vaccines

In first tests made according to the constant serum method the antigenicity of monovalent vaccines of Types O, A and C given s/c in doses of 0.5 ml. was compared with that of trivalent vaccine containing equal volumes of the monovalent samples. Since the trivalent vaccine was inoculated in doses of 0.5 and 0.25 ml. (see above), the respective mice received 3 and 6 times less

Table 1

CCT with serum pools from mice treated with monovalent or trivalent vaccines (constant serum method)

MIS pools			Titration of free C' ml MS-Ag-C' mixture													AM 0.06-0.3 ml
Mice treated with vaccine	MIS dil.	Ag	.06	.08	.1	.12	.14	.16	.18	.2	.22	.24	.26	.28	.3	
monoval. 0 - 8172 0.5 ml	1 : 2	O	87+	12	6	0	0									8.1
	1 : 4	O	50	6	0	0										4.3
monoval. A - 8216 0.5 ml	1 : 2	A	94	87	75	50	25	25	12	12	6	0	0			29.7
	1 : 4	A	87	37	25	6	0	0								11.9
monoval. C - 8327 0.5 ml	1 : 2	C	100	94	87	75	62	50	50	37	25	25	25	12	6	49.8
	1 : 4	C	100	87	75	50	37	12	6	6	0	0				25.8
trival. I 0.25 ml	1 : 2	O	75	37	12	6	0	0								10.0
		A	100	94	75	50	37	25	12	12	12	12	6	0	0	33.5
		C	100	87	37	25	12	12	6	0	0					21.5
	1 : 4	O	75	25	6	0	0									8.2
		A	62	37	12	6	0	0								9.1
		C	37	6	0	0										3.3
trival. I 0.5 ml	1 : 2	O	100	100	100	100	94	94	94	94	87	87	87	75	75	91.3
		A	100	100	100	100	100	100	94	94	94	87	87	87	75	93.7
		C	100	100	100	100	94	87	75	75	62	62	62	50	50	78.2
	1 : 4	O	100	87	75	62	37	25	12	12	6	6	0	0		32.6
		A	100	94	75	62	50	37	25	12	6	6	0	0		35.9
		C	100	87	75	50	37	12	6	6	0	0	0			28.8

+ unlysed cells (%)

antigen per virus type than animals treated with monovalent vaccines. Both monovalent and trivalent pools were tested in 1 : 2 and 1 : 4 dilutions against Ag of Types O, A and C. Mixtures of monovalent MIS (1 : 2) with Ag of heterologous virus types and 10 % C′ (1 : 1 : 2) caused complete hemolysis in amounts of 0.06 ml., and normal mouse serum (MNS) 1 : 2 reacted negatively with all three antigens. These readings as well as the complete hemolysis shown by the serum, antigen and C′ controls (2) are not recorded in Table 1.

The table shows a dose-effect correlation, which originally was the main subject of this experiment. An unexpected result was the stronger reaction of trivalent MIS compared with that of the monovalent pools, which was particularly striking with the pool from mice receiving 0.5 ml. of trivalent vaccine I. A 1 : 2 dilution of this pool reacted so strongly with antigens of all three types that endpoints were not reached with 0.3 ml. MS-Ag-C′ mixture in the titration of free C′.

Table 2 shows the result of a CCT made according to the serum dilution method with serum pools from mice treated with different doses of trivalent vaccines I and II. Results obtained with trivalent vaccine I are comparable with those of a similar test made with monovalent vaccines O-8172, A-8216 and C-8327 recorded in Table 5 of a preceding paper (2). The stronger antigenic effect of trivalent vaccine I when given in a 0.5 ml. dose is again evident.

Trivalent vaccine II stimulated antibody formation very poorly in doses of 0.75 ml. A dose of 1.5 ml. provoked a fair antibody response to Type O

Table 2

CCT with serum pools from mice treated with trivalent vaccines (serum dilution method)

MIS pools		Test for free C′						Mean percentages of unlysed cells *
Mice treated with vaccine	MIS dil.	Ag O		Ag A		Ag C		
		ml MS-Ag-C′ mixture						
		0.08	0.1	0.08	0.1	0.08	0.1	
I 0.25 ml	u	100 +	94	100	100	100	100	O : 29 A : 43 C : 30
	1 : 2	62	37	100	87	94	37	
	1 : 4	37	6	87	37	25	6	
	1 : 8	6	0	6	0	0	0	
	1 : 16	0	0	0	0	0	0	
I 0.5 ml	u	100	100	100	100	100	100	O : 56 A : 63 C : 57
	1 : 2	100	100	100	100	100	100	
	1 : 4	100	100	100	100	100	100	
	1 : 8	37	12	87	62	62	12	
	1 : 16	12	0	12	0	6	0	
	1 : 32	6	0	0	0	0	0	
	1 : 64	0	0	0	0	0	0	
II 0.75 ml	u	25	12	0	0	6	0	O : 4 A : 0 C : 0.5
	1 : 2	6	0	0	0	0	0	
	1 : 4	0	0	0	0	0	0	
II 1.5 ml	u	100	100	6	0	100	94	O : 37 A : 0.5 C : 26
	1 : 2	100	100	0	0	75	37	
	1 : 4	37	6	0	0	6	0	
	1 : 8	0	0	0	0	0	0	

* in serum dilution range u — 1:32 with respective antigen (0.08 plus 0.1 ml MS-AG-C' mixture)

\+ unlysed cells (%)

antigen and a weaker one to Type C antigen, whereas there was hardly any reaction with antigen of Type A.

CCT with sera from individual mice treated with monovalent vaccines

The purpose of this experiment was to study the antibody response of individual mice to weak and to strong monovalent vaccines of Types O, A and C. Tests were made according to the serum dilution method using the same reagents throughout with the exception of sheep erythrocytes (preserved in ALSEVER solution), which did not always come from the same animal. However, C′ titrations made with every newly prepared hemolytic system gave rather uniform results. Serum titrations were made against homologous Ag.

The figures given for every serum in Table 3 represent arithmetical means (AM) of estimated percentages of unlysed cells in 12 tubes of the serum dilution range u (undiluted) to 1 : 32 (0.08 plus 0.1 ml. MS-Ag-C′ mixture). The figures at the bottom of Table 3 are AM of the figures calculated for individual mice (24 per vaccine).

Table 3

CCT with serums from individual mice treated with monovalent vaccines (serum dilution method using homologous antigen)

Vaccine (0.5 ml)					
O - 2340 pb 1.1	O - 8172 pb 4	A - 2306 pb 2	A - 8216 pb 12	C - 2302 pb 2.7	C - 8327 pb 5.9
0 +	0	3	0	0.5	16
0	0	4	0.5	0.5	18
0	0.5	4	0.5	0.5	30
0	1	9	0.5	1	31
0	1	9	4	1	36
0	2	12	6	4	37
0	5	12	8	4	42
0.5	6	12	10	5	44
1	9	13	17	6	46
1	9	14	19	10	48
1	10	14	21	12	53
2	11	19	24	13	54
4	15	21	29	14	59
4	15	22	31	15	59
4	15	22	32	16	62
5	19	23	36	20	63
6	27	23	41	23	65
7	30	24	47	23	67
8	32	25	50	24	70
8	40	34	54	26	71
9	47	34	58	26	73
25	52	34	60	29	77
30	53	37	61	30	78
42	62	38	62	46	87
Arithmetical means (%)					
6.6	19.2	19.2	28.0	14.6	53.6

+ mean percentage of unlysed cells in serum dilution range u — 1:32 (0.08 plus 0.1 ml MS-Ag-C′ mixture)

As Table 3 shows, there was marked individual variation in the antibody response of mice to a given vaccine. Vaccine C-8327 was the strongest antigen which stimulated antibody formation in all mice, the mean percentages of unlysed cells fluctuating between 16 and 87 per cent. A poor stimulant of antibody synthesis was vaccine O-2340, which provoked fair antibody titers (25—42 %) in 3 animals only. Low titers ranging from 0.5 to 9 % were recorded for 14 mice, and zero readings were made in 7 cases. Striking individual differences in immune response are also evident from the values listed for the other vaccines. AM calculated for the various vaccines (see bottom of Table 3) agreed qualitatively with their pb ("puissance bovine") values (2).

In the experiment just described, all mixtures of undiluted or diluted MIS with homologous Ag and 10 %C′ subjected to cold fixation were tested for free C′ in quantities of 0.04, 0.06, 0.08 and 0.1 ml., but mean values were calculated from results obtained with the two largest volumes only (2). By doing so, minute amounts of antibody which may have been present in sera from vaccinated mice were purposely ignored. Since it is of interest in this connection to know whether or not vaccinated mice for which zero values are recorded in Table 3 developed any antibodies at all, results obtained from 0.04 and 0.06 ml. volumes of mixtures of undiluted serum, Ag and 10 % C′

Table 4

Supplementary test of weak MIS* using 0.04 and 0.06 ml MS-Ag-C′ mixture

Serum donors vaccinated with	Mouse No.	Mixture with homologous antigen		Mixture without antigen (serum control)	
		ml MS-Ag-C′ mixture			
		0.04	0.06	0.04	0.06
O-2340	1	62 +	12	50	6
	2	75	12	12	0
	3	50	6	37	0
	4	75	12	25	0
	5	50	6	12	0
	6	50	12	12	0
	7	50	12	12	0
O-8172	1	50	6	12	0
	2	62	6	37	0
A-8216	1	37	0	25	0

* giving zero readings with 0.08 and 0.1 ml MS-Ag-C′ mixture (see Table 3)
\+ unlysed cells (%)

are listed separately in Table 4 together with values recorded for the corresponding serum controls, which contained buffered saline instead of Ag. As can be seen in the table, there was evidence of trace amounts of antibody in practically all of the sera listed.

CCT with sera from individual mice treated with trivalent vaccines

Sera from mice vaccinated with different doses of trivalent vaccines I and II were tested undiluted and in twofold serial dilutions against O,A and C antigens using the serum dilution method. Due to insufficient quantity, the serum from one animal (marked** in the table) vaccinated with 1.5 ml. of vaccine II could not be tested. For the same reason, the serum from another mouse inoculated with 0.5 ml. of vaccine I was tested only in dilutions of

Table 5

CCT with serums from individual mice treated with trivalent vaccines in different doses (serum dilution method)

Vaccine I 0,25 ml			Vaccine I 0.5 ml			Vaccine II 0,75 ml			Vaccine II 1.5 ml		
O *	A *	C *	O	A	C	O	A	C	O	A	C
0 +	0.5	0	0	0	0	0	0	0	0	0	0
0	10	5	1	12	1	0	0	0	0	0	0
0	20	37	2	22	8	0	0	0	0	0	0
0,5	17	26	17	34	16	0	0	0	0	0	0
2	8	8	18	41	31	0	0	0	0,5	0	0
3	6	3	20	19	46	0	0	0	1	0	1
3	13	31	21	26	37	0	0	0	1	0	2
4	6	9	27	55	35	0	1	2	2	0	0
5	1	4	28	36	25	0,5	0	0	2	0	22
7	8	11	30	47	26	0,5	0	1	18	0	1
10	20	10	31	60	67	1	0,5	0	19	0	0
11	34	26	43	57	50	1	1	0	21	0	14
21	23	41	47	52	57	1	0	4	23	0	23
23	43	35	49	48	64	2	1	1	24	0	0
24	20	24	49	53	59	2	0	9	24	0	26
32	53	30	59	44	52	4	0	1	26	0,5	23
33	14	37	63	56	67	7	0	5	30	0	26
33	34	34	68	84	65	11	0	5	32	8	37
34	25	37	73	58	67	15	0	0	38	1	19
44	52	54	73	75	70	15	1	1	39	0	4
52	72	49	75	70	73	27	0	0	51	1	19
65	70	75	75	78	34	31	0	0	59	7	53
71	83	69	77	60	66	34	0	11	65	0	27
85	55	49	82	94	71	40	2	17	**	**	**
Arithmetical means (%)											
23.4	28.6	28.9	42.8	49.2	45.3	8.0	0.3	2.4	20.7	0.8	12.9

* Ag

\+ mean percentage of unlysed cells in serum dilution range u — 1:32 (0.08 plus 0.1 ml MS-Ag-C' mixture)

** not enough serum

1 : 2—1 : 64 (see top of columns 3—6 in Table 5). Zero readings recorded for this serum do therefore not necessarily mean that the animal had not produced any antibodies at all. In any case, this serum was very weak towards Ag of all three types.

The results presented in Table 5 again reveal marked individual differences in antibody response to the same dose of vaccine. Serums from mice responding well to vaccine I had relatively high titers towards all three Ag. Other serums reacted better with Ag of one type than with those of other types, and some animals developed antibodies poorly towards all three types. Vaccine II was inferior to vaccine I. Antibody formation was extremely poor towards Type A. A dose-effect correlation is recognizable with each antigenic component of both vaccines. Both, the numbers of well-responding mice and the mean serum titers were higher within groups of mice receiving the larger doses.

Titration of the most potent monovalent and trivalent MIS encountered

Titrations of relatively potent MIS according to the serum dilution method allow an estimation of the numbers of mice to be used in potency tests of monovalent and trivalent FMD vaccines. For this purpose, results obtained with 9 monovalent and 4 trivalent sera of high potency are presented in Tables 6 and 7, respectively.

As can be seen in Table 6, tubes containing 0.08 ml. MS-Ag-C′ mixture with serum dilution 1 : 32 showed small amounts of unlysed cells in 4 cases, whereas corresponding tubes with 0.1 ml. mixture showed a trace of unlysed cells in one case only.

In only 2 of 144 titrations of monovalent sera, tubes containing 0.1 ml. mixture with serum dilution 1 : 32 had a similar small residue of unlysed cells. The serum donors had been inoculated with vaccine C-8327.

The strongest trivalent MIS from mice receiving 0.5 ml. of vaccine I were slightly more active in higher dilutions (seeTable 7). However, tubes containing 0.1 ml. MS-Ag-C′ mixture with serum dilution 1 : 64 always showed complete hemolysis. This was also the case in the remaining serum titrations listed in Table 4. The recipients of vaccine II failed to produce sera reacting in dilutions higher than 1 : 16.

Table 6

CCT with relatively strong sera from individual mice treated with 0.5 ml monovalent vaccine (serum dilution method)

MIS			Test for free C′ ml mixture		AM *	MIS			Test for free C′ ml mixture		AM *
Vacc.	Mouse No.	Dil.	0.08	0.1	%	Vacc.	Mouse No.	Dil.	0.08	0.1	%
O 8172	27	1 : 4	100+	100	70	A 8216 cont.	130	1 : 4	100	100	67
		1 : 8	94	87				1 : 8	87	75	
		1 : 16	37	6				1 : 16	37	6	
		1 : 32	12	0				1 : 32	0	0	
		1 : 64	6	0		C 8327	72	1 : 4	100	100	62
		1 : 128	0	0				1 : 8	87	50	
	74	1 : 4	100	100	70			1 : 16	6	0	
		1 : 8	100	100				1 : 32	0	0	
		1 : 16	25	6			95	1 : 4	100	100	70
		1 : 32	6	0				1 : 8	100	87	
		1 : 64	0	0				1 : 16	37	12	
A 8216	63	1 : 4	100	100	76			1 : 32	0	0	
		1 : 8	100	87			117	1 : 4	100	100	72
		1 : 16	75	37				1 : 8	100	100	
		1 : 32	12	6				1 : 16	37	25	
		1 : 64	0	0				1 : 32	6	0	
	129	1 : 4	100	100	85			1 : 64	0	0	
		1 : 8	100	100			141	1 : 4	100	100	57
		1 : 16	100	94				1 : 8	50	25	
		1 : 32	25	0				1 : 16	6	0	
		1 : 64	0	0				1 : 32	0	0	

* Arithmetical means of unlysed cells in MS dilution range u — 1:32 (0.08 and 0.1 ml MS-Ag-C' mixture)

\+ unlysed cells (%)

Table 7

CCT with relatively strong serums from individual mice treated with 0.5 ml trivalent vaccine I (serum dilution method)

MIS		Test for free C'						Mean percentage of unlysed cells *
		Ag O		Ag A		Ag C		
Mouse No.	Dil.	ml MS-Ag-C' mixture						
		0.08	0.1	0.08	0.1	0.08	0.1	
1	1 : 2	100 +	100	100	100	100	100	O : 68 A : 84 C : 65
	1 : 4	100	100	100	100	100	94	
	1 : 8	94	50	100	100	94	37	
	1 : 16	50	12	94	62	37	12	
	1 : 32	6	0	37	12	6	0	
	1 : 64	0	0	6	0	0	0	
2	1 : 2	100	100	100	100	100	100	O : 75 A : 70 C : 73
	1 : 4	100	100	100	100	100	100	
	1 : 8	100	94	100	75	100	100	
	1 : 16	75	25	50	12	50	25	
	1 : 32	12	0	6	0	0	0	
	1 : 64	6	0	0	0	0	0	
3	1 : 2	100	100	100	100	100	100	O : 73 A : 75 C : 70
	1 : 4	100	100	100	100	100	100	
	1 : 8	100	62	100	100	94	75	
	1 : 16	62	12	75	25	50	12	
	1 : 32	37	6	6	0	6	0	
	1 : 64	6	0	0	0	0	0	
4	1 : 2	100	100	100	100	100	100	O : 82 A : 94 C : 71
	1 : 4	100	100	100	100	100	100	
	1 : 8	100	100	100	100	100	100	
	1 : 16	100	75	100	100	37	12	
	1 : 32	12	0	87	37	6	0	
	1 : 64	6	0	12	0	0	0	

* in serum dilution range u — 1:32 with respective antigen (0.08 plus 0.1 ml MS-Ag-C' mixture)

\+ unlysed cells (%)

Discussion

Results described above show that trivalent vaccine I stimulated antibody formation more than the three monovalent vaccines from which it was prepared. This happened in spite of the fact that the mice inoculated with monovalent vaccines received three times more antigen per type than the recipients of the trivalent mixture. Such a potentiating effect was not anticipated, otherwise a different dosage would have been chosen. We are not aware of any reports in the FMD literature describing a similar phenomenon in other species. On the contrary, French investigators (3) state that they observed in cattle and guinea pigs neither synergism nor antagonism between the various compounds of trivalent vaccines. The synergic effect was a sideline observation in the present work and requires more intensive study, which should show whether or not the phenomenon is confined to mice and how frequently it occurs in this species.

As the most effective monovalent vaccine incorporated in the trivalent mixture, C-8327 experienced only a slight increase in potency when mixed

with vaccines O-8172 and A-8216. On the other hand, the antigenicity of the A and O vaccines increased considerably by mixing. The effect was most marked with vaccine O-8172, the weakest of the group in a relative sense. This synergic effect would probably have been still greater in mice inoculated with 1.5 ml. of trivalent vaccine I, a dose corresponding to the dosage of the monovalent vaccines. We suspect that the potentiating effect was in some way correlated with the high potency in mice of vaccine C-8327 (see Tables 3 and 5), which may have boosted the antigenicity of the other vaccine components.

Compared with trivalent vaccine I, results obtained with vaccine II were rather disappointing. The weak reactions may have in part been due to antigenic differences between the production strains of this vaccine and the strains used here for preparation of Ag for CCT. However, it is difficult to believe that antigenic diversity alone accounted for the extremely poor reactions obtained with Ag of Type A.

In view of the results recorded in Table 4 and of other observations, it seems unlikely that individual differences in antibody formation by vaccinated mice are primarily due to differences in the threshold of antigenic stimulation. It rather appears that there is considerable variation in the capacity to respond to an antigenic stimulus. In this respect, the intensity of the stimulus appears to be significant, since a potent vaccine like C-8327 provoked a good antibody response in the great majority of the treated mice (see last column in Table 3). It can be seen in the first column of the same table that exceptional animals may react rather strongly even to a weak antigen like vaccine O-2340. In general, the number of mice showing a good antibody response was proportional to the potency of the vaccine (see Table 3) and to the dose as shown in Table 5.

For routine potency tests of FMD vaccines in mice, titration of individual serums from vaccinated animals with calculation of AM would not be practical. It is preferable to test pools from groups of mice inoculated with a standard dose of vaccine, but it is then important to know how many mice should be used per vaccine. This question can now be answered on the basis of titration results obtained in CCT with the most potent monovalent and trivalent serums encountered (see Tables 6 and 7). When 0.1 ml. amounts of MS-Ag-C′ mixture are tested for free C′ in CCT according to the serum dilution method, 32 mice will be adequate for monovalent vaccines, whereas 64 animals will be required for trivalent vaccines. For trivalent vaccines of low potency, 32 mice would be sufficient, but it would be practically impossible to predict the quality of the vaccines. With the numbers of mice just mentioned, grossly false results are not to be expected from MIS pools containing individual serums of exceptionally high potency. The numbers of mice used heretofore were obviously too small.

For experienced personnel it is easy to obtain small quantities of mouse blood, e. g. 0.3 ml. per animal, from large groups of mice within a short time. Pools, of course, should contain equal amounts of blood from all animals of the respective groups.

Summary

Trivalent foot-and-mouth disease vaccine (O-A-C) prepared from monovalent FRENKEL-type vaccines (IFFA, Lyon), stimulated the formation of complement-fixing antibodies in mice to a greater extent than the monovalent vaccines in spite of the fact that these contained 3 times more type-specific antigen per dose. The potentiating effect was less marked with the most potent

vaccine (C) than with two weaker vaccines (A and O) incorporated in the trivalent mixture.

Another trivalent vaccine produced abroad was less effective in mice, its Type A component being particularly weak.

Antibody responses of individual mice receiving the same doses of vaccine varied within wide limits. Individual differences in the capacity to respond to an antigenic stimulus appear to be responsible. In general, the antibody response was proportional to the antigenic potency of a vaccine and to the dose. A monovalent vaccine, highly potent in mice, stimulated antibody synthesis in all of 24 mice with high serum titers in the majority of the animals.

Titration results obtained with the strongest individual sera indicate that 32 mice are adequate for potency tests of monovalent vaccines and 64 mice for trivalent vaccines.

Zusammenfassung

Antikörperbildung bei Mäusen nach Verabfolgung monovalenter oder trivalenter Maul- und Klauenseuche-Vaccinen.

Trivalente Maul- und Klauenseuche-Vaccine (O-A-C), hergestellt aus monovalenten FRENKEL-Vaccinen (IFFA, Lyon), bewirkte bei Mäusen stärkere Bildung von komplementbindenden Antikörpern als die einzeln geprüften monovalenten Impfstoffe, obwohl diese 3mal mehr typspezifisches Antigen pro Dosis enthielten. Der Steigerungseffekt war weniger markant bei der stärksten im trivalenten Gemisch enthaltenen Vaccine (C) als bei den beiden schwächeren Komponenten (A und O).

Eine andere ausländische trivalente FRENKEL-Vaccine war wesentlich weniger wirksam, was besonders für deren A-Komponente zutraf.

Nach Verabreichung der gleichen Vaccinedosis variierte die Antikörperbildung bei Einzelmäusen in starkem Maße. Dies scheint auf individuell verschiedener Reaktionsfähigkeit auf einen Antigenreiz zu beruhen. Im allgemeinen bestand eine Proportionalität zwischen Antikörperbildung einerseits und der antigenen Wirksamkeit einer Vaccine sowie der Vaccinedosis andererseits. Eine bei Mäusen besonders kräftige monovalente C-Vaccine stimulierte bei allen von 24 Mäusen die Antikörpersynthese, wobei die meisten Seren hohe Titerwerte erreichten.

Mit stärksten Einzelseren erzielte Titrationsergebnisse ließen erkennen, daß für die Wirksamkeitsprüfung bei monovalenten Vaccinen 32 Mäuse und bei trivalenten 64 Mäuse je Impfstoff ausreichen.

Resumé

Formation d'anticorps chez les souris après l'application des vaccins antiaphteux monovalents et trivalents

Un vaccin antiaphteux trivalent (O-A-C), mélange de trois vaccins monovalents FRENKEL (IFFA, Lyon), provoque chez les souris une plus forte formation d'anticorps fixant le complément que les vaccins monovalents individuels, quoique ces derniers contiennent par dose trois fois plus d'antigène spécifique que le vaccin trivalent. L'effet synergique était moins prononcé avec le vaccin le plus fort (C) qu'avec les deuc valences plus faibles (A et O) du mélange trivalent.

Un autre vaccin trivalent étranger (O-A-C) préparé selon la méthode FRENKEL est beaucoup moins efficace, ce qui concerne surtout la valence A.

La formation d'anticorps varie fortement chez les souris individuels vaccinés avec la même dose. Il parait que c'est causé par variation indivi-

duelle dans la capacité de réagir à une stimulation antigénique. On observe une relation entre la formation d'anticorps d'une part et l'efficacité antigénique des vaccins et la dose d'autre part. Un vaccin C spécialement efficace pour souris provoque la formation d'anticorps dans touts les animaux, la plupart des serums atteignants des titres hauts.

La titration des serums les plus forts montre que 32 souris suffisent pour l'épreuve de l'efficacité de vaccins monovalents, tandis qu'un vaccin trivalent nécessite 64 souris.

Resumen

La producion de anticuerpos en lauchas despues de inoculacion de vacunas monovalentes o trivalentes contra fiebre aftosa

Vacunas trivalentes contra la fiebre aftosa (O-A-C), fabricadas a base de vacunas monovalentes por el método de FRENKEL (IFFA, Lyon), produjeron en lauchas anticuerpos de fijación del complemento más fuertes que en las vacunas monovalentes. Esto efecto de aumento de la fijación ha sido más marcante con los dos componentes más débiles (A y O) que con el componente más fuerte (C).

Otra vacuna (FRENKEL) trivalente, extranjera, ha sido mucho menos eficaz, lo que se deve a su componente A.

La aplicación de dosis iguales de vacunas ha producido formación de anticuerpos diferentes en cada ratón aisladamente. La causa de esto parece ser la capacidad individual diferente de reacción frente el estímulo de lo antígeno. Por lo general, hubo una proporción entre la produción de anticuerpos y la eficacia de los antígenos de una vacuna por un lado, y la dosis de vacuna por el otro lado. Una vacuna (C) monovalente especialmente poderosa ha estimulado en 24 ratones la síntesis de anticuerpos, cujos sueros han alcanzado un alto título.

Con los sueros aislados más fuertes, para que los resultados de la titulación fueran reconocibles en la prueba de la eficacia han sido suficientes 32 ratones para vacunas monovalentes y 64 ratones para las vacunas trivalentes.

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