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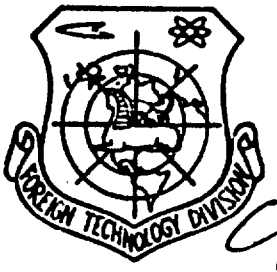
FOREIGN TECHNOLOGY DIVISION

INVESTIGATION OF THE METHOD OF AEROSOL IMMUNIZATION WITH POWDER PLAGUE VACCINE ON WIDE CONTINGENTS OF PEOPLE

by

N. I. Aleksandrov, N. Ye. Gefen,
K. G. Gapochko, et. al.



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К к	*К к*	K, k	Ъ ъ	*Ъ ъ*	"
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М м	*М м*	M, m	Ь ь	*Ь ь*	'
Н н	*Н н*	N, n	Э э	*Э э*	E, e
О о	*О о*	O, o	Ю ю	*Ю ю*	Yu, yu
П п	*П п*	P, p	Я я	*Я я*	Ya, ya

*ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ё in Russian, transliterate as yё or ё. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

GREEK ALPHABET

Alpha	A	α		Nu	N	ν	
Beta	B	β		Xi	Ξ	ξ	
Gamma	Γ	γ		Omicron	O	o	
Delta	Δ	δ		Pi	Π	π	
Epsilon	E	ε	ϵ	Rho	P	ρ	ϱ
Zeta	Z	ζ		Sigma	Σ	σ	ς
Eta	H	η		Tau	T	τ	
Theta	O	θ	ϑ	Upsilon	T	υ	
Iota	I	ι		Phi	φ	Φ	ϕ
Kappa	K	ϰ	κ	Chi	X	χ	
Lambda	Λ	λ		Psi	Ψ	ψ	
Mu	M	μ		Omega	Ω	ω	

RUSSIAN AND ENGLISH TRIGONOMETRIC FUNCTIONS

Russian	English
sin	sin
cos	cos
tg	tan
ctg	cot
sec	sec
cosec	csc
sh	sinh
ch	cosh
th	tanh
cth	coth
sch	sech
csch	csch
arc sin	$\sin^{-1}$
arc cos	$\cos^{-1}$
arc tg	$\tan^{-1}$
arc ctg	$\cot^{-1}$
arc sec	$\sec^{-1}$
arc cosec	$\csc^{-1}$
arc sh	$\sinh^{-1}$
arc ch	$\cosh^{-1}$
arc th	$\tanh^{-1}$
arc cth	$\coth^{-1}$
arc sch	sech^{-1}
arc csch	csch^{-1}
rot	curl
lg	log

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INVESTIGATION OF THE METHOD OF AEROSOL IMMUNIZATION WITH POWDER PLAGUE VACCINE ON WIDE CONTINGENTS OF PEOPLE

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(Received 26 September 1962)

Successful testing of the method of aerosol immunization against plague on limited contingents of people was carried out in 1961 with the authorization and recommendation of the Serum-Vaccine Committee of the Ministry of Health of the USSR to lead to more widespread testing.

While performing this work we simultaneously solved several problems, particularly the approval of the technique for mass aerosol immunization with powder plague vaccine under practical conditions, the verification and refinement of the data obtained earlier which indicated the harmlessness and low reactogenicity of this method of immunization, and also the comparison of the reactogenicity, (api) immunological effectiveness of the aerosol method of vaccination with the reactogenicity and and immunological effectiveness of the subcutaneous and epicutaneous methods of administering a living plague vaccine.

In addition, in a comparative aspect we studied the single and double schemes for administering the plague vaccine.

For the aerosol immunization we used a dry living powder plague vaccine made from the EV strain.

The vaccination was conducted in normal rooms 30 m^3 and 112 m^3. At the time of the administrations of the immunization 10-190 persons were accomodated in these room simultaneously.

The preparation was continuously atomized during the course of the administration. During the immunization in the room with the small volume, in the process of selecting the optimum dose of the preparation, 3 to 30 g of vaccine were atomized. During the massive vaccination which took place in the large room, the outflow of preparation was 10-12 g. The duration of the immunization cycle was 25 minutes (preparation - 10 minutes, vaccination - 15 minutes).

The aerosol immunization was administered to 716 persons. Before the vacinnation we conducted their medical examination, including a detailed inspection, analyses of the blood and urine, and also a roentgenoscopy of the chest organs. The contingent subjected to the immunization was composed of virtually healthy people. Of these persons who were innoculated, 26 had been vaccinated subcutaneously with the EV vaccine two years earlier.

After the vaccination medical supervision was established for those immunized.

The state of health of the 550 persons innoculated by the aerosol method was traced for a year, up to the present time, and some deviations from the norm were recorded in them.

An examination of those persons immunized during the first eight days after the vaccination included daily thermometry, interrogation for the purpose of explaining subjective sensations, hemotological and roentgenoscopic investigations. The blood sampling and the roentgenoscopy were conducted on the 1st-2nd, 3rd-4th, 7th-8th day of observation. In each of these

time periods we examined an average of 50 persons.

The immunological effectiveness of the vaccination was evaluated by setting up intracutaneous allergic tests with pestin*, manufactured in the Saratovsk Anti-Plague Institute. The other test which we used was the determination of the titer of specific antibodies in the hemagglutination reaction according to the Levi technique. The testing with pestin and the titer determination of the antibodies were carried out on the 7th, 30th, and 90th days after the vaccination.

With the inhalation of 8-195 million microbes of the EV strain there were no post-vaccinal reactions in any of the 716 immunized people. An increase in the inhaled dose to 200-300 million microbes caused the manifestation of general post-vaccinal reactions, which, however, were recorded rarely (in 3 of the 100 immunized) and proceeded in a light (2%) or average (1%) form (with respect to weight) with an increase in temperature to 37.2-38°. These reactions completely pass after 12-36 hours.

No local reactions to the immunization appeared on the part of the respiratory organs.

In the majority of people subjected to the aerosol vaccination we noted shifts in the state of the prescribed elements of the blood, expressed primarily in the change in the quantity of leukocytes (Table 1). Even after 1-2 days in the absolute majority of those innoculated (87%) the quantity of leukocytes grew; in addition, in half of the cases this increase exceeded the boundary of the physiological norm (9000 per 1 mm^3) and should be valued as leukocytosis. Three-four days after the vaccination we observed a tendency toward a reduction in the number of leukocytes in part of those persons innoculated (in 40% of the examined cases the number of leukocytes was lower than the initial level, in 36.5% - somewhat higher and in 23.5% - at the same level). Leukocytosis was recorded only in 13.5% in this time period.

*Unfound word [пестин].

Table 1

Results of the investigation of the hemograms of persons subjected to aerosol immunization with powder plague vaccine

Examination period (in days)	Number of persons examined	Changes in the number of leukocytes after immunization						Changes in the ROE after immunization				All persons with changes	
		decrease	without change	increase			average	decrease	without change	increase		abs. no.	%
				501–5000	more than 5000	total				up to 10 mm per hour	more than 10 mm per hour		
Before immunization	157	—	—	—	—	—	7 000	—	—	—	—		
1–2nd	54	5 (9,3%)	2 (3,7%)	39	8	47 (87%)	8 536	19	20	15	1	52	96,3
3rd	52	21 (40%)	12 (23,5%)	17	2	19 (36,5%)	7 665	21	12	14	—	44	84,6
7–8th	51	7 (13,7%)	4 (7,9%)	27	13	40 (78,4%)	9 745	16	15	23	2	47	92,1

Note: 1. For the lower boundary of the norm we accepted 5000, for the upper - 9000 leukocytes per 1 mm. For the upper boundary of ROE (sedimentation rate) for men - 10 mm per hour.

A count of the leukocytes, taken on the 7th-8th days after the vaccination, again indicated a sharp increase in their number, recorded in 78.4% of those innoculated; in addition, in almost half of the cases this was valued as pronounced leukocytosis. It should be emphasized that the degree of increase in this period was more pronounced than in the earlier examination periods: on the 7th-8th days the average number of leukocytes per 1 mm^3 was 9745, at the same time on the 1st-2nd days after the immunization this factor was 8536.

Sharp changes with respect to the leukocytes in those persons vaccinated were also noted during the countings of the leukocytic formula. These changes were pronounced in the increase in the number of neutrophils with a relative decrease in the number of lymphocytes. An increase in the number of neutrophils is accompanied by a shift to the left because of the stabnuclear forms. A pronounced and constant increase in the number of monocytes was characteristic.

A significant change in the settling rate of the erythrocytes was not noted in any of the examination periods.

The data obtained during the course of the hematological examinations of those persons vaccinated indicate that in the majority of persons a general ster-otyped reaction, pronounced in the changes in leukocytes, developed in response to the immunization.

The setting up of intracutaneous tests with pestin preceded the investigation of this preparation, whose purpose was to determine the specificity of the reactions caused by it in those persons innoculated. The data obtained from 130 non-immunized persons revealed the absence of pronounced nonspecificity of the reactogenicity of the preparation. Positive reactions were recorded in only 7 persons (5.4%). Similar results were obtained in experiments on guinea pigs.

The aerosol vaccination with powder plague vaccine caused a sharp immunological reorganization in those persons innoculated, which was manifested both in an increase in the sensitivity to pestin and in an accumulation of specific antibodies (Table 2).

Table 2

Results of the setting up of intracutaneous tests with pestin and the determination of the titer of the antibodies in those persons vaccinated by the aerosol method[1]

Day of examination	Tests with pestin					Hemagglutination reaction		
	Number of persons examined	Total positive reactions	+	++	+++	Number of persons examined	Total positive reactions	Average titer of antibodies
7-th	12	11	—	4	7	11	8	1:10
30-th	31	16	4	9	3	14	14	1:123
90-th	10	5	1	2	2	5	4	1:5

[1]T.G. Abdullin, K.I. Volkovoy, M.I. Koshʻyan and Yu.N. Zakharov took part in the study of immunological effectiveness.

In addition to this we undertook an investigation whose purpose was to study the reactogenicity and immunological effectiveness of a double aerosol vaccination and to compare it with the reactogenicity and immunological effectiveness of the other schemas and methods of administering a living plague vaccine (single aerosol, single and double epicutaneous and subcutaneous).

The double aerosol vaccination was given with a 5-day interval. The dose of the first vaccination was an average of 200 million microbes, the dose of the second - 100-200 million microbes. To obtain comparable data a group of people were simultaneously innoculated one time with a powder vaccine with a 200-300 million microbe dose.

For subcutaneous and epicutaneous vaccinations we used vaccines from the Irkutsk Anti-Plague Institute (series No. 34) and the Saratovsk Anti-Plague Institute (series No. 3). With a double vaccination the interval between administrations of the preparation was 7 days. With a subcutaneous immunization we administered, according to instructions, one human dose of the vaccine the first time and 0.6 human dose the second time. The epicutaneous vaccination was given in accordance with real instruction.

The most pronounced immunological reorganization was recorded in persons vaccinated twice by the aerosol and subcutaneous methods; the second most pronounced - in those vaccinated once by these methods. The immunological effectiveness of the single and double epicutaneous vaccination was lower than with the first two methods of vaccine application (Table 3).

The reactogenicity of the vaccination methods examined by us differed significantly (Table 4). The sum percentage of the general reactions to the single aerosol vaccination did not exceed 3; in addition, not one strong reaction was recorded. Repeated aerosol vaccination caused the manifestation of general postvaccinal reactions somewhat more often (10%); in addition, in

Table 3

Characteristics of the immunological effectiveness of various methods and schemas of immunization against plague

Method of immunization	Frequency	Interval (in days)	Vaccine dose (billions of microbes)	Result on different days after immunization															
				7 th					30-th					90- th					
				Hemagglutination reaction			Test with pestin		Hemagglutination reaction			Test with pestin		Hemagglutination reaction			Test with pestin		
				Number examined	Number of positive reactions	Average titer	Number examined	Number of positive reactions	Number examined	Number of positive reactions	Average titer	Number examined	Number of positive reactions	Number examined	Number of positive reactions	Average titer	Number examined	Number of positive reactions
Aerosol	1	—	0,2																
	2	5	0,3 I—0,2	11	8	1:10	12	11	14	14	1:123	12	7	5	4	1:5	10	5
Subcutaneous	1	—	II—0,I—0,2	15	11	1:50	17	17	13	12	1:140	12	7	3	3	1:35	11	7
	2	7	1 human-dose 1+0,6 human-dose	9 16	5 10	1:18 1:40	15 9	12 9	19 13	19 10	1:92 1:203	14 17	4 12	8 8	5 4	1:19 1:18	11	4
Epicutaneous	1	—	1 human-dose	3	1	0	5	2	7	6	1:60	8	2	11	9	1:10	15	5
	2	7	1+1 human-dose				2	1	10	8	1:52	18	4					

Table 4

Characteristics of the reactogenicity of various methods and schemas of immunization against plague

Method of immunization	Frequency of inoculation	Interval (in days)	No. of the vaccine series	Dose (in millions of microbes)	Number inoculated	Number of post-vaccinal reactions: general — weak abs. no.	weak %	average abs. no.	average %	strong abs. no.	strong %	total abs. no.	total %	local abs. no.	local %
Aerosol	1	—	14	200—300	100	2	2	1	1	—		3	3	—	
	2	5	14	100—200	80	3	3,7	1	1,3	4	5	8	10	4	5
Subcutaneous	1	—	34	1 human-dose	232	57	24,6	31	13,4	7	3	95	41	22	95
				ditto	100	8	8	25	25	66	66	100	100	98	98
			3	» »	100	15	15	23	23	54	54	92	92	100	100
Subcutaneous	2	7	34	0,6 human-dose	135	28	20,8	6	4,4	4	2,9	38	28,1	128	96
Epicutaneous	1	—	34	1 human-dose	5600	96	1,7	120	2,1	—		116	3,8	5376[2]	96
	2	7		ditto	20	—		—		—		—			

[1]The graph gives data characterizing the reactogenicity of the maximum doses of aerosol vaccine since only these doses were studied using tests with pestin and the hemagglutination reactions were determined at this stage to be optimum. In the remaining 616 persons innoculated with smaller doses of aerosol, but not examined by immunological tests, there were no reactions to the vaccination.

[2]Local reactions during repeated vaccination were not considered.

half of them the reaction was evaluated as strong. With respect to the clinical picture the reaction did not differ from the reaction to the first vaccine aspiration. With repeated administration of the vaccine we noted the manifestation of local reactions (in 5% of those innoculated), which proceed in the background of the general reaction and manifest themselves in the form of light laryngotracheites, which disappeared immediately after the reduction in body temperature to the normal level.

Subcutaneous innoculations were significantly more reactogenic. With a single administration of one human dose (2 billion microbes for the given series) the general post-vaccinal reactions (depending on the series of the preparation) were recorded in 41-100%; in addition, in 16.4-92% of the persons vaccinated they were evaluated as of average severity and as serious. The general post-vaccinal reactions, which appeared in response to the subcutaneous administration of the preparation, did not differ, with respect to the clinical picture, from the reactions to the aerosol vaccination; however, their symptoms were significantly more pronounced and they continued to be serious, being accompanied by the complete lack of work capability on the 1st, 2nd, and 3rd days. A local reaction to the subcutaneous innoculation (infiltrate and soreness at the place of the administration, regional lymphadenitis) was observed in the absolute majority of persons vaccinated (95-100%) and continued for 2-7 days.

Repeated subcutaneous administration of a decreased dose of vaccine (1.2 billion microbes) caused general reactions in a smaller percentage of cases (28). Local reactions were observed, as before, regularly (96%).

The reactogenicity of the epicutaneous method of immunization was studied from the results of the mass single vaccination of 5600 persons. General reactions were observed in 3.6%, local - in 9% of those innoculated. Repeated epicutaneous vaccination did not cause general reactions.

The data given lead to the conclusion that the most pronounced sero-allergic shifts are recorded in the persons innoculated twice, with the aerosol and subcutaneously; however the reactogenicity of the aerosol method of vaccination is immeasurably lower than the reactogenicity of the subcutaneous method. The epicutaneous method of immunization, with respect to general reactogenicity, corresponded to the aerosol, however, with respect to the number of local reactions significantly exceeded it and yielded to it with respect to the level of sero-allergic reorganization which appeared.

CONCLUSIONS

1. The single aerosol immunization of people with powder plague vaccine was accompanied by a weak general reaction.

2. ~~The~~ double aerosol vaccination of people, carried out with a short interval between innoculations (5 days), was characterized by a somewhat higher reaction compared with the single vaccination. The reaction was significantly less pronounced than with a subcutaneous vaccination.

3. The epicutaneous method of immunization, with respect to number and intensity of general reactions, corresponded to the single aerosol, but with respect to local reactogenicity it significantly exceeded the aerosol.

4. The most pronounced sero-allergic shifts were noted in those persons who were innoculated twice; in addition the immunological effectiveness of the aerosol method of vaccination corresponded to the immunological effectiveness of the subcutaneous method. The immunological effectiveness of the single and double epicutaneous immunization is lower than the aerosol and subcutaneous.

5. ~~We need to make~~ a further and more in-depth comparative study* of the reactogenicity and immunological effectiveness of the aerosol, subcutaneous and epicutaneous methods of immunization against plague.

* should be made

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