EPIDEMIOLOGICAL EFFECTIVENESS OF LIVE VACCINE AGAINST INFLUENZA DURING THE PERIOD OF THE OUTBREAKS OF A2 AND B INFLUENZA IN 1962

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EPIDEMIOLOGICAL EFFECTIVENESS OF LIVE VACCINE AGAINST INFLUENZA DRUING THE PERIOD OF THE OUTBREAKS OF A2 AND B INFLUENZA IN 1962

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For obtaining a regular and reliable effect from the use of a live vaccine against influenza it is necessary to use a specific preparation of a guaranteed quality containing a highly immunogenic virus. It is also very important that the correct method of applying the vaccine be used, including the triple administration of the preparation by means of pulverization in the upper respiratory tract and the maximum extent of immunization of susceptible contingents (Smorodintsev and Korovin, 1961; Smorodintsev et al., 1961; Smorodintsev, 1962; Smorodintsev et al., 1962).

The present work was started in the end of 1961, prior to the large-scale influenza outbreak in January--April, 1962. The epidemic took place in the form of two successive waves. Of these, the first was cuased by the virus of influenza type A2 (January--February, 1962), and the second -- by the virus of type B (March--April, 1962). Under the specified conditions a significant difference was observed in the incidence of vaccinated and nonvaccinated persons.

The immunization was carried out with the lyophilized live influenza vaccine produced by the Leningrad Institute of Vaccines and Sera, and put out in the form of a monovaccine of type A2 (series No 181) and of type B (Series No 194). The concentration of virus in the series of vaccines used corresponded to the instruction requirements and comprised 7 lg10 for type A2 vaccine and 5 lg10 for type B.

Before use the dry monovalent vaccine was diluted with boiled water which had been cooled to room temperature or distilled water in a ratio of 1:2.5 (5ml of water per 2 ml of vaccine). After dissolving, the vaccines of types A2 and B were incorporated in equal volumes into a divaccine. Here the end dilution of each monovaccine equaled 1:5.

Following the triple administration of the resulting divaccine to 83 adults who had a low antibody content in the blood prior to immunization (1:10 and lower), in 3 weeks following the final immunization a fourfold and higher increase of antibodies was noted in 59% in respect to type A2 and in 64% in respect to type B1, which corresponded to the instruction requirements of the Serum-Vaccine Committee of the USSR Ministry of Public Health.

The inoculations were performed by means of administering 0.25 ml of diluted divaccine A2 + B or monovaccine of type A2 or B into the nasal passage with the help of a barbershop metallic sprayer. Prior to vaccination the nasal passages were cleaned of mucus (by blowing), and following administration of the vaccine the inoculated person remained with his head thrown back for 2--3 minutes.

All the sprayers used were preliminarily checked and graduated, that is, a determination was made of how many compressions of the rubber bulb were necessary for administering 0.25 ml of the preparation.

In October--November 1961, young men (19--21 years old) from organized collectives were subjected to immunization. For increasing the effectiveness of the immunization each collective was inoculated completely with live vaccine. As a control there were other analogous collectives in which active immunization was not carried out at all or in which they used monovaccines of one of the two serological types -- A2 or B. During the period of the type A2 influenza epidemic it was possible to study the effectiveness in 14 collectives in which the inoculations were performed with divaccine or A2 vaccine. The total number of men was 12,601. In the 10 control collectives there were 16,052 men who had not been inoculated at all or who had been inoculated with type B vaccine. Under observation during the period of the B influenza outbreak were 12 collectives which had been immunized with divaccine or monovaccine type B (10,473 persons) and 21 collectives which had not been inoculated at all or were inoculated with A2 vaccine (18,180 persons).

Observations of the inoculated and noninoculated persons began immediately following the conclusion of inoculations, that is, beginning with January 1962. These included the obligatory hospitalization of all persons who had an increase in temperature and influenza-like symptoms. All the persons who fell ill were subjected to hospitalization but only those who had the appropriate diagnosis were considered under the heading of influenza.

During the period of the type A2 influenza outbreak from 15 January through 25 February and the subsequent type B influenza outbreak in March--April 1962 a selective laboratory investigation was carried out on influenza stricken persons from both the vaccinated and nonvaccinated contingents. The laboratory investigation included a virological study of the secretion of the nasal cavity, taken on the 1--3rd day of illness and injected into the amniotic cavity of 10--11 day old chick embryos. Paired sera from patients, taken during the acute period of the disease and after 2--3 weeks from the onset of illness, were investigated in the hemagglutination inhibition reaction with human erythrocytes of the O group, which were added after twofold dilutions of the sera with 4 AU of antigen (diagnostic agent type A2 produced by the Leningrad Institute of Vaccines and Sera) were maintained for 18 hours at 4°.

The data on morbidity was collected on each individual collective of inoculated and noninoculated contingents. We considered all the cases with

a clinical diagnosis of influenza. They were summarized by decades. In order to ensure a well-founded summation of the data based on the morbidity of individual collectives by groups of inoculated and noninoculated persons, we determined the dates for the onset and conclusion of the outbreak for each collective. Increases in the indices of morbidity for each decade over 5 per 1000 (0.5%) were considered as the onset of the outbreak. By an analogous method we determined the date for the conclusion of the outbreak, being guided by a lowering of morbidity for a decade to an index of 5 per 1000.

Since the average duration of an outbreak of influenza A2 and B in 1962 was contained in two decades based on individual collectives, we conditionally considered an increase in the number of cases of influenza for 2 decades of more than 10 per 1000 persons as the index for an increase in morbidity. In a number of collectives increased incidence with influenza A2 and B was recorded over a period of 3 decades, and less often - during 1 decade.

In this manner we ascertained the number of cases in each separate collective during the epidemic influenza A2 in January -- February, and influenza B in March--April 1962

When analyzing the dynamics of the influenza A2 and B outbreaks in the groups of vaccinated and nonvaccinated persons, we used, in chronological order, the data based on total influenza incidence for 2 decades of the preepidemic period (December 1961--January 1962) and for 3 decades of the rise in influenza for each outbreak.

In a number of collectives, particularly among those which were vaccinated, no rise at all was noted in incidence above the previously stated normal level (5 per 1000 for one decade). This was accepted conditionally as 0. The proportion of such favorable collectives in the control group turned out to be considerably less than in the group which was encompassed by massive immunization.

During the period of the first wave of influenza in January--February 1962, 12 strains of the A2 influenza virus were isolated from the 29 patients investigated. The bond between this wave of incidence and the type A2 influenza virus was supported by the results of investigating 141 paired sera; in 121 of these, that is, in 85.5%, an increase of 4 times and more was noted in the antibodies to the type A2 influenza virus.

In March--April 1962, negative results were obtained during the virological investigation of 60 patients. This was supported by other data throughout Leningrad, testifying to the exceptionally low isolation rate of the type B influenza virus in the epidemic of 1962. At the same time, during the serological investigation of paired sera from 137 patients with the B14 vaccine strain, in 101 cases a positive result was obtained (73.6%). This substantiated the bond of the second wave of influenza in March--April 1962 with the type B influenza virus. An increase of antibodies to the influenza virus in patients during this period was noted only in rare cases.

We divided the results of studying incidence among inoculated and non-inoculated into the two outbreaks of type A2 and B which were observed.

In table 1 we present the data on influenza incidence among inoculated and noninoculated contigents during the period of the first wave of influenza type A2.

Out of the 14 collectives in which vaccination was not carried out entirely, or where the type B monovaccine was used for inoculation, outbreaks of very high intensity (more than 200 cases per 1000) were noted in one, of high intensity (100-199 cases per 1000) - in one, of moderate intensity (50--99 cases per 1000) - in 2, and of low intensity (10--49 cases per 1000) - in 5 collectives. In 5 collectives there was no rise in incidence. A completely different distribution of influenza outbreaks based on intensity was noted for the same period of the first wave of type A2 in the 19 control collectives with a total strength of 16,052 men. Here in the predominant number of collectives (12 out of 19) a very high (8 collectives) and high (4 collectives) intensity of outbreaks was recorded. Moderate and low intensity outbreaks were recorded in 6 collectives and in only one collective there was no rise in influenza.

The results of the observations of the intensity of morbidity among inoculated and noninoculated groups during the period of the influenza B outbreak are presented in table 2. During this period the differences in the intensity of morbidity between the inoculated and control collectives were expressed more clearly than during the type A2 outbreak. In the 12 collectives in which 10,473 men were vaccinated, there were no outbreaks of a very high, high, and moderate intensity. There were only 4 collectives with a low incidence rate of 10--49 cases per 1000; in the remaining 8 collectives no rise in influenza was recorded.

Comparative data of the 21 collectives containing 18,180 men, where the vaccinations were not carried out at all or where they were performed with type A2 monovaccine, testified to the completely different distribution in the intensity of outbreaks of type B influenza: In 7 collectives a very high and high incidence was noted, in 8 collectives - a moderate and low incidence, and in the remaining 6 collectives no rise in morbidity was observed.

Completely analogous results were obtained when processing the data on incidence in inoculated and noninoculated collectives during the periods of the type A2 and B outbreaks depending on the strength of the collectives. We broke all the collectives down into 3 groups: 1st - less than 500 persons, 2nd - more than 500 but less than 1000 persons, and 3rd - collectives containing more than 1000 men. It turned out that very clear divergences in the intensity of influenza infection among inoculated and noninoculated persons did not depend on their absolute numbers. The greatest divergences in the average indices of morbidity for the outbreaks of A2 and B were noted in the largest collectives, where the influence of such factors as turnover of personnel, irregularity of contacts, etc., is displayed with lesser uniformity. The average index of type A2 influenza incidence per 1000 men

in the 5 largest inoculated collectives with a total numerical strength of 6,767 persons comprised 6.7. In the 5 control collectives with a total numerical strength of 8,006 persons, the average index reached 139.6 per 1000. Lesser divergences during the period of the outbreak of type A2 influenza were noted in collectives with an average and small numerical strength.

During the period of the outbreak of type B influenza the differences in the average indices of morbidity between noninoculated and inoculated were displayed very clearly in each group of collectives which differed according to numerical strength.

Table 3 and figure 1 present the total data on the apportionment of the number of collectives with a various intensity of outbreaks, with a demonstration of the great frequency of strongly infected collectives in the noninoculated groups and the comparative rarity of such cases in the inoculated collectives during the period of the type A2 influenza epidemic, and their complete absence during the period of the type B influenza.

Figure 2 presents the dynamics of morbidity among inoculated and noninoculated groups during the period of the first and second wave, indicating the significant differences in incidence among inoculated and noninoculated groups in the various periods of January--February, when the epidemic of A2 influenza took place, and March--April 1962 when the outbreak of type B influenza was observed.

In the epidemiological observations organized by us, the effectiveness of live influenza vaccine was shown with sufficient reliability, with the exception of the influence of accidental factors.

A good quality of preparation and exactness in carrying out the inoculations are compulsory conditions for the effective application of live vaccine against influenza. The feasibility of analyzing the results obtained is determined by the thorough and complete exposure of all cases of influenza among the inoculated and noninoculated groups.

Conclusions

1. The qualitative performance and timely completion, prior to the onset of a regular outbreak, of a triple immunization encompassing the largest number of collectives, must be considered the main conditions for exposing the epidemiological effectiveness of live influenza vaccine.

2. We were able to study the results of the immunization of 12,600 adult persons, distributed among 33 separate collectives, during two successive epidemics of influenza type A2 and B in January -- April 1962.

3. In January--February 1962 in the majority of these collectives an outbreak of type A2 influenza took place, and beginning with March a wave of influenza type B emerged. During this a significantly more intense incidence rate with type A2 and B influenza was observed in the control noninoculated collectives than in the collectives which were encompassed by the almost complete administration of live influenza vaccine.

Literature

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Table 1

Intensity of influenza morbidity among inoculated and noninoculated groups during the period of the wave of type A2 influenza (January - February 1962)

Noninoculated	Number of collective		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
	Number of persons in collective		400	900	760	415	242	440	980	420	400	350	903	1600	640	1200	710	550	836	2000	1 306	15 052
	Number sick with influenza	absolute	193	834	216	110	64	108	220	89	72	55	114	184	50	80	47	26	35	20	0	2 517
		per 1000 persons	482,5	488,9	284,2	265	264,1	245,4	211,9	108	157	157	126,2	115	78,1	66,6	66,1	47,2	41,6	10	0	156,8
Inoculated	Number of collective		20	21	22	23	24	25	26	27	28	29	30	31	32	33						
	Vaccine		A2B	A2B	A2B	A2	A2	A2B	A2	A2B	A2	A2B	A2B	A2B	A2B	A2						
	Number inoculated	absolute	752	489	744	800	799	800	1300	1150	1478	350	900	1600	1239	200						
		%	94	98	78,3	100	84	100	100	100	100	100	100	100	80,1	100						
	Number sick with influenza	absolute	225	64	61	58	39	28	18	13	15	0	0	0	0	0						
		per 1000 persons	299,2	130,8	82,0	72,5	48.8	35,0	13,8	11,3	10,1	0	0	0	0	0						

1 = Inoculations with monovaccine type B

0 - here and in table 2, morbidity in the range of 5 cases per 1000 men for a decade.

Table 2

Intensity of influenza morbidity among inoculated and noninoculated groups during the period of the wave of type B influenza (March - April 1962)

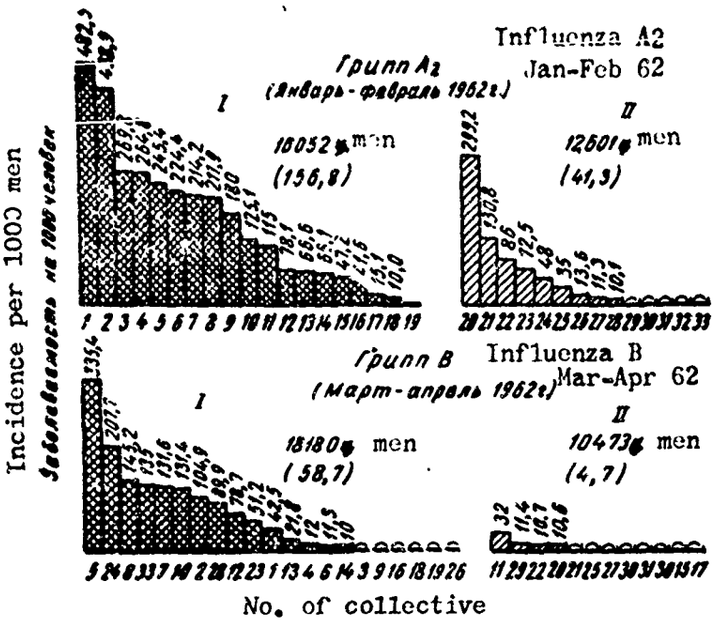
																							Total
Noninoculated	No. of collective		5	24[1]	8	33[1]	7	10	2	28[1]	12	23[1]	1	13	4	6	14	3	9	16	18	19	26[1]	
	Number of persons in collective		242	759	420	200	880	350	1 900	1 478	1 600	800	400	640	415	440	1 200	760	400	550	2 000	1 306	1 300	18 180
	Number sick with influenza	absolute	86	166	61	27	129	46	199	133	126	41	17	15	0	0	12	0	0	0	0	0	0	1 056
		per 1000 persons	355,4	207,7	145,2	135	131,6	131,4	104,9	89,9	78,7	51,2	42,5	23,4			10	0	0	0	0	0		58,7
Inoculated	No. of collective		11	29	22	20	21	25	27	30	31	32	15	17										
	Vaccine		B	A2B	A2B	A2B	A2B	A2B	A2B	A2B	A2B	A2B	B	B										
	Number inoculated	absolute	903	350	744	752	489	800	1150	900	1600	1239	710	836										10 473
		%	70,3	100	78,3	94	98	100	100	100	100	90,1	87,6	41,6										
	Number sick	absolute	29	0	8	8	0	0	0	0	0	0	0	0										45
		per 1000 men	32,1		10,7	10,6	0	0	0	0	0	0	0	0										4,7

1 - Inoculated with monovaccine type A2

Table 3

Distribution of various quantitative levels of incidence with influenza type A2 and B among vaccinated and control persons

Period of epidemic 1962	Composition of collectives	Number of		Number of collectives with various levels of incidence				
		Collectives	Persons	very high (+ 200)	high (100-199)	moderate (50 - 99)	low (10 - 49)	absent (less than 10)
Outbreak of A2 influenza	Noninoculated	19	16 052	8	3	3	4	1
	Inoculated	14	12 601	1	1	2	3	5
Outbreak of B Influenza	Noninoculated	21	18 180	2	5	3	5	6
	Inoculated	12	10 473	-	-	-	4	8



156.8 , 41.3 ..... average indices of incidence per 1000 men

Figure 1. Intensity of influenza incidence in indices per 1000 among persons inoculated and noninoculated with live influenza vaccine

I - noninoculated; II - inoculated.

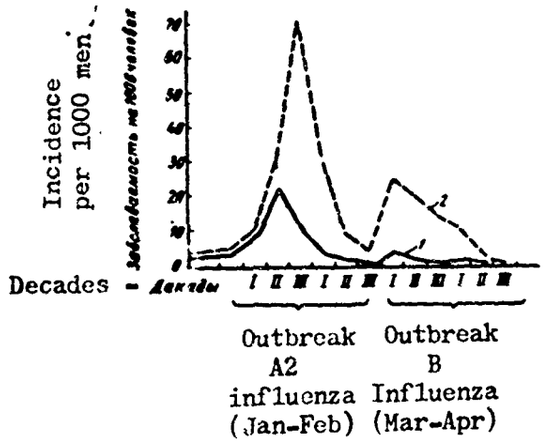


Figure 2. Influenza incidence among inoculated and noninoculate men in 1962.
1 - inoculated; 2 - noninoculated.