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Evaluation of the Effectiveness of Large-Scale Vaccination against Influenza in the USSR *

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Vaccination is at present the only means of influenza control; so far, large-scale trials of live vaccine have been made mainly in the USSR. This paper discusses such a trial in persons above 12 years of age.

About 40% of the population of Smolensk and about 50% of the population of the nearby town of Jarcevo were vaccinated with live influenza vaccine in the winters of 1964-65 and 1965-66, and the incidence of influenza and other acute respiratory diseases in these towns during the 1965 epidemic and the 1966 pre-epidemic period was compared with that in nearby "control" towns. Most subjects were vaccinated 2 or 3 times with divalent A2-B vaccine in 1964, but some only once; in 1965-66, most subjects were vaccinated once with monovalent B vaccine and once with divalent A2-B vaccine.

Analysis of the incidence data for the towns involved, of more detailed incidence data for about 30 000 workers and 4000 schoolchildren in Smolensk and one control town, and of a controlled trial involving about 4000 persons, indicated that the large-scale vaccination led to a reduction in incidence of about 1.5- to 2-fold in 1965 and of about 2- to 3-fold in 1966. Limited serological studies in 1966 indicated that the reduction in incidence in the group studied was not 3-fold but 4-fold. The rather low protection offered by the 1964 vaccination may have been due to the low immunogenicity of the vaccine, or to the fact that the vaccine strains used did not correspond exactly to the influenza virus strains circulating in nature.

Vaccination with live or killed influenza vaccine is at present the most promising method of influenza control. A 2-fold to 3-fold reduction in the morbidity from influenza and other acute respiratory diseases (ARD) may on the average be expected after vaccination with live influenza vaccine (Solokov, 1954; Ždanov et al., 1958; Smorodincev & Korovin, 1961).

It has been repeatedly reported that the index of effectiveness [1] of influenza vaccine is directly proportional to the number vaccinated in the community in question, reaching values of 4-7 when 70%-90% of the working population have been vaccinated (Sokolov, 1954; Davenport et al., 1955).

In most investigations, the effectiveness of the vaccine has been estimated by studying the incidence of the disease among the vaccinated and unvaccinated members of different sections of the community (workers, schoolchildren, etc). The question of the possible effect of mass influenza vaccination on the epidemic process was first raised by Slepuškin et al. (1962) in connexion with an investigation undertaken in 1959-61.

The present study deals mainly with the effectiveness of large-scale vaccination with live divalent influenza vaccine containing vaccine strains A2 and B in industrial centres in the Smolensk region during the winters of 1964-65 and 1965-66.

MATERIALS AND METHODS

Vaccine

The vaccine was prepared by the Moscow Institute for Research on Virus Preparations. In 1964, six batches of live influenza vaccine were prepared from virus strain A2/Krasnodar 101/59 and six batches

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[1] The index of effectiveness is defined as:
morbidity from influenza and other ARD in the unvaccinated
morbidity from influenza and other ARD in the vaccinated

from the strain B/Moscow/Lih/59; the placebo batch, 320A2, consisted of the constituents of the vaccine minus the virus. The vaccine was diluted before administration so that 0.5 ml of the final preparation contained 0.1 ml (the required dose) each of vaccines A2 and B. This vaccine was used for the vaccinations in November and December 1964.

The strains used for the preparation of the vaccine for the winter of 1965-66 were A2/England 12/64 and B/Romania 1/63, which had the advantage of being antigenically more similar to the strains circulating in nature. In view of the possibility of an outbreak of B influenza in the spring of 1966, subjects were vaccinated first with monovalent influenza B vaccine and later with divalent A2-B vaccine.

The vaccination campaign

The towns chosen for vaccination were Smolensk and Jarcevo, both with large concentrations of light and metal-working industry. Children under 14 years formed between 25% and 28% of the population. Vaccination campaigns covering the population aged 12 years and over were carried out in November and December 1964 and from December 1965 to January 1966. The vaccine was administered intranasally with the aid of Sahov-Orlova instillators.

In 1964, a total number of 97 464 persons were vaccinated, accounting for 40.5% of Smolensk's population and 51% of Jarcevo's. In 1965-66, 100 359 persons were vaccinated, i.e., 41.3% of the population of Smolensk and 52% of that of Jarcevo.

Vaccinations were carried out 3 times at intervals of 8 to 14 days in 1964, and twice in 1965-66.

Controls

Nearby industrial centres where no influenza vaccination was carried out were selected as controls to allow evaluation of the effectiveness of the vaccination. The control towns for Smolensk were Vitebsk and Kaluga, both of which had roughly the same industrial structure, total population and age distribution of population. The control towns for Jarcevo were Safonovo and Roslavl', which had similar populations and age distributions but a somewhat different industrial structure.

Recording of the results

Starting in November 1964, a daily record of the incidence of influenza was kept in Smolensk, Jarcevo and the control towns.

A special card index was also compiled to allow more accurate registration of cases of influenza among vaccinated and unvaccinated subjects in 15 schools or factories, starting from 1 November 1964. Each card gave the date of onset, diagnosis (" influenza " or " acute catarrh of the respiratory tract ") and duration of the case, according to the medical certificates delivered. This survey covered about 34 000 subjects.

Further, a controlled trial covering 4335 subjects was carried out in certain factories in 1964-65. Shifts of workers working under comparable conditions were selected at random and given either vaccine or placebo. The results of this trial were processed by standard statistical methods (Hill, 1955).

Laboratory and clinical tests

Haemagglutination-inhibition tests. Haemagglutination-inhibition tests were performed on paired sera from workers in two large factories who were suffering from influenza or ARD (for diagnostic purposes), and from 30-50 subjects vaccinated with each series of vaccine (for estimating the immunogenicity of the vaccine); in the latter case the sera were sampled before vaccination and 30 days after the last vaccination. The tests were performed according to routine techniques, using standard antigens of influenza A2 and B virus prepared by the Institute of Epidemiology and Microbiology, Kazan' and antigens of the vaccine strains A2/Krasnodar 101/59, B/Moscow/Lih/59, B/Romania 1/63, A2/England 12/64 and (from the second half of 1965) A2/Gor'kij 62/65.[1]

Isolation of virus. Nasopharyngeal washings taken from some patients were inoculated into the amniotic cavity of chick embryos for isolation of the virus.

Reactogenicity and take rate. The temperature of from 40 to 200 persons vaccinated with each batch of vaccine and with the placebo was recorded daily for 5 days in order to determine the reactogenicity.

Nasopharyngeal washings from 20-30 persons vaccinated with each series were tested 3 times (on the second, third and fourth days after vaccination) for the take of the vaccine on the nasopharynx.[2]

[1] We would like to thank Dr G. V. Eremeev for the preparation of the antigens for A2/England 12/64, A2/Gor'kij 62/65 and B/Romania 1/63, and Dr B. M. Pariž and Dr L. A. Porubel' for supplying the antigens for A2/Krasnodar 101/59 and B/Moscow/Lih/59, and the placebo.

[2] The take rate is defined as the percentage of the persons tested in whom virus could be reisolated from the nasopharynx on the second, third or fourth day after vaccination.

TABLE 1
INCIDENCE RATES DUE TO INFLUENZA AND OTHER ARD IN TOWNS COVERED BY VACCINATION CAMPAIGN AND IN TOWNS WHERE NO VACCINATION WAS GIVEN, DURING THE 1962 AND 1965 EPIDEMICS AND THE 1966 PRE-EPIDEMIC PERIOD

Town	Vaccination coverage in 1964 and 1965-66 (%)	Incidence rate (%)							Percentage reduction in incidence between 1962 and 1965	Weekly incidence at height of 1965 epidemic (%)
		1962	1965			1966				
			Total	Among children [a]	Among adults [b]	Total	Among children [a]	Among adults [b]		
Kaluga	0	23.4	23.1	26.3	19.8	11.6	16.2	10.1	1.3	8.1
Vitebsk	0	27.2	22.1	40.5	17.0	9.5	21.0	5.9	18.8	7.1
Smolensk	about 42	19.0	12.8	23.8	8.7	5.9	15.7	3.0	32.6	3.6
Roslavl'	0	18.0	15.5	35.6	14.9	4.7	8.5	3.7	13.9	5.8
Safonovo	0	15.7	14.0	19.1	13.6	6.1	8.9	4.6	10.8	6.9
Jarcevo	about 52	18.3	14.0	21.4	10.0	4.2	8.7	2.4	23.5	4.3

[a] Below 14 years of age.
[b] Over 14 years of age.

The washings were concentrated on chick erythrocytes, and 0.2 ml of inoculum was introduced into the amniotic cavity of chick embryos according to the technique described by Gorbunova & Sokolov (1960).

RESULTS

Epidemiological trends

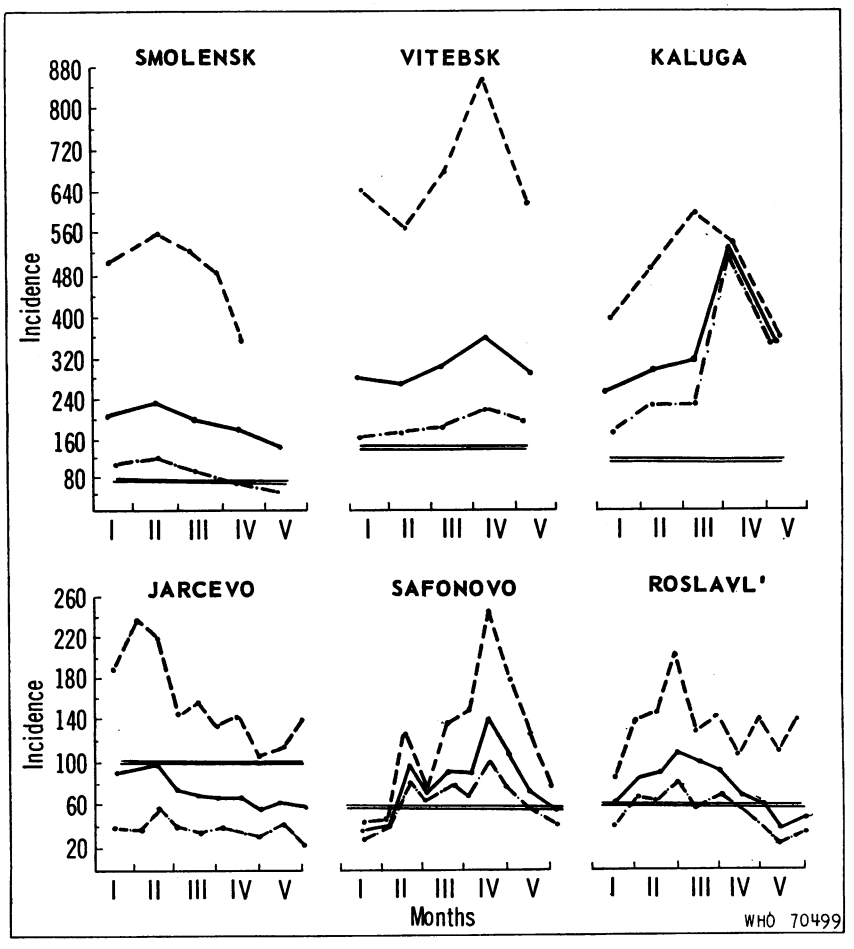
No appreciable shifts in morbidity were observed in November-December 1964; early in 1965 a slight increase in the incidence of influenza and other respiratory diseases was recorded, mainly among children. An influenza epidemic, lasting 1½ months, broke out in the last week of January both in the control towns and in Smolensk and Jarcevo.

Comparison of the incidence of influenza in the towns where vaccination campaigns were and were not held (Table 1) shows that the incidence was somewhat lower in all towns during the 1965 epidemic than during the 1962 epidemic. However, the

TABLE 2
INFLUENZA AND ARD MORBIDITY DURING THE 1962 AND 1965 EPIDEMICS IN CERTAIN FACTORIES IN SMOLENSK AND VITEBSK

Town	Type of factory	Vaccination coverage (%)	Incidence (%)		Percentage reduction in incidence between 1965 and 1962
			1962	1965	
Smolensk	Clothing	54.8	31.1	20.7	33.0
	Knitted goods	54.8	25.8	15.0	41.9
	Flax	54.9	29.6	17.9	37.4
	Automation equipment	70.1	25.1	9.9	60.1
	Furniture	65.6	21.1	10.7	49.3
	Building materials	73.0	29.0	11.7	59.7
Vitebsk	Clothing	0	29.0	26.6	8.4
	Knitted goods	0	28.4	23.2	18.0
	Carpets	0	21.7	20.4	6.0
	Electrical measuring instruments	0	21.2	20.1	5.2
	Furniture	0	20.5	19.3	6.3
	Prefabricated houses	0	29.7	23.9	19.5

INCIDENCE OF INFLUENZA AND OTHER ARD IN VARIOUS TOWNS IN THE PERIOD JANUARY-MAY 1966, PER 10 000 POPULATION [a]



[a] The graphs for Smolensk, Vitebsk and Kaluga show the *monthly* incidence rates per 10000, and those for Jarcevo, Safonovo and Roslavl' the *half-monthly* incidences for the period ending at the point in question. The curves for children refer to persons below 14 years of age, and those for adults to persons over 14 years.

decrease in incidence during the epidemic period was only about 18.8% in Vitebsk and 1.3% in Kaluga as compared with 1962, while in Smolensk it was 32.6%, i.e., twice as much as in Vitebsk and more than 20 times as much as in Kaluga. A similar situation was found in Safonovo and Jarcevo (decrease in incidence 10.9% and 23.5% respectively).

Analysis of the age distribution of the incidence of influenza showed that the above-mentioned trends in morbidity were mainly associated with changes in the incidence among adults (over 14 years). Thus, the incidence of the disease among children in Smolensk and Kaluga was almost the same, whereas among adults in Smolensk it was half that in Kaluga and Vitebsk. This difference was less marked in Jarcevo, but even here the incidence of influenza was 20%-25% lower than in the control towns. The survey of influenza and other ARD in a number of factories

in Smolensk and Vitebsk also supported this conclusion. In 1965, the morbidity rate in the factories in Smolensk was 33%-60% less than in 1962 (Table 2), while in Vitebsk it was 5%-20% less.

Analogous trends in the morbidity rate were encountered after the vaccination compaigns in the winter of 1965-66. During the period of observation lasting from January to May 1966, an increase of 1.5-fold to 2.5-fold in the morbidity rate was recorded in all the control towns (see the accompanying figure). On the other hand, a gradual decrease in morbidity down to the summer level was noted in Smolensk and Jarcevo beginning from the second half of February, the time of the highest degree of post-vaccination immunity. At the same time, the number of cases of acute respiratory diseases in Smolensk somewhat exceeded the average level during the same period of the previous interepidemic in 1964.

Study of the age distribution of the incidence in 1965-66 (Table 1) showed that, just as in 1964-65, the morbidity rate among the adult population of Smolensk and Jarcevo was 1.5 to 3 times lower than in the corresponding control towns, whereas children exhibited almost the same rate in all corresponding towns. The general morbidity rate in the Smolensk factories which were studied in detail was 1.5 to 2.5 times lower than in the same branches of industry in Vitebsk and Kaluga.

Controlled trial

The morbidity among unvaccinated workers in all 3 shifts involved in the controlled trial did not differ significantly from that among the subjects who received placebo, while the groups vaccinated with mixtures of two different batches of vaccines A2 and B both showed a reduction in the morbidity rate which was significant at the 0.01 probability level. The results of the controlled trial are summarized in Table 3.

Detailed survey of selected factories and schools

The above observations indicate the possibility of evaluating the effectiveness of the vaccines by comparing the morbidity among vaccinated and unvaccinated workers in the same factories. Our study of the morbidity rate in vaccinated and unvaccinated groups among 30 000 workers (Table 4) showed that the effectiveness of the vaccine depends upon the following factors: (1) the vaccination coverage, (2) the number of vaccinations per subject and (3) the branch of industry. The morbidity rate among 2691 persons who for some reason or other received only one vaccination did not significantly differ from that among the unvaccinated workers, whereas the morbidity rate among persons who were vaccinated twice was 1.4-fold lower, and that among persons who were vaccinated three times was 1.6 lower, than the morbidity rate in the unvaccinated group. These differences are statistically significant.

The highest effectiveness was recorded in the metal-working and building-materials industries, where over 55% of the workers were vaccinated: the index of effectiveness for subjects who received 3 vaccinations was 1.9. In addition, the average period of confinement to bed owing to influenza or ARD was half a day to a day less in the group of persons who received 3 vaccinations than in the unvaccinated group.

TABLE 3

RESULTS OF CONTROLLED TRIAL OF INFLUENZA VACCINE

Vaccine series used	Number of persons in group	Incidence (%)	Index of effectiveness	Difference in incidence between vaccinated subjects	
				and subjects receiving placebo	and unvaccinated subjects
162A2 + 128B	1 058	9.2	1.5	4.1 [a]	5.1 [a]
144A2 + 130B	1 196	8.7	1.6	4.6 [a]	5.6 [a]
320A2 (placebo)	939	13.3	1.1	—	1.0
Unvaccinated	1 142	14.3	—	—	—

[a] Statistically significant at 0.01 probability level.

TABLE 4

INFLUENCE OF VACCINATION COVERAGE AND NUMBER OF VACCINATIONS PER PERSON ON INCIDENCE OF INFLUENZA AND OTHER ARD IN CERTAIN BRANCHES OF INDUSTRY IN SMOLENSK AND JARCEVO DURING THE 1965 EPIDEMIC

Branch of industry	Vaccination coverage (%)	Vaccination status	Number of persons in group	Incidence during whole epidemic (%)	Average duration of invalidity (days)	Index of effectiveness of vaccine
Light industry	45-55	once	1 001	19.7	6.5	1.1
		twice	1 895	16.4	7.7	1.3
		three times	5 597	14.8	5.2	1.4
		unvaccinated	4 390	21.1	5.9	—
Light industry	56-80	once	1 187	16.8	4.6	1.3
		twice	3 232	15.2	5.7	1.4
		three times	3 372	13.3	5.4	1.6
		unvaccinated	1 066	21.9	6.4	—
Metal-working and construction	56-80	once	503	17.5	4.9	1.0
		twice	2 159	12.0	5.1	1.5
		three times	3 958	8.9	4.6	2.0
		unvaccinated	2 483	17.6	4.9	—
Total	65	once	2 691	18.0	5.4	1.1
		twice	7 286	14.5	6.1	1.4
		three times	12 927	12.5	5.1	1.6
		unvaccinated	7 939	20.0	5.7	—

Approximately the same results were obtained in the survey of schoolchildren in Smolensk: the morbidity among 3845 children who were vaccinated 3 times was 1.9-fold lower than that among 5133 unvaccinated children.

Effect of vaccination performed 2 years in succession

Data on the effect of vaccination in 1964 or 1965-66, or both, on the morbidity rate for influenza in the early months of 1966 are given in Table 5. It will be seen that in the period February-April 1966 the number of cases of influenza and other ARD was 1.9-fold less in the 18 656 persons who had been vaccinated twice in 1965-66 than in the 6740 persons who were not vaccinated in 1965-66. However, it should be taken into account that 2627 of these unvaccinated persons were vaccinated twice or three times in 1964; it would therefore be more correct to compare the morbidity rate among vaccinated persons with that among the 4113 people who were not vaccinated in either year. This is also done in Table 5, where the group of vaccinated persons is further subdivided into 12 002 who were vaccinated in both years, 6654 vaccinated only in 1965 and 2627 vaccinated only in 1964.

It will be seen that persons vaccinated in both years exhibited the highest (2.7-fold) reduction in morbidity rate, while a 2-fold reduction in morbidity rate was observed among persons vaccinated either only in 1964 or only in 1965-66. The average duration of the disease among persons vaccinated in 1965-66 and taken ill during the observation period was shorter by 0.5 day than among unvaccinated persons.

Serological data

The evaluation of the effect of vaccination on the basis of the recorded morbidity rate due to influenza and other acute catarrhs of the respiratory tract (ACRT) was supplemented by a serological investigation of 63% of the workers in two factories who contracted influenza or other ACRT. The results of

TABLE 5

INFLUENCE OF VACCINATION WITH LIVE INFLUENZA VACCINE IN 1964 AND 1965-66 ON INCIDENCE OF INFLUENZA AND OTHER ARD IN THE PERIOD FEBRUARY-APRIL 1966 [a]

No. of times vaccinated in 1964	No. of persons in group	Incidence (%)	Average duration of invalidity (days)	Index of effectiveness of vaccine	Reduction in incidence on vaccination	Mean error of reduction	Statistical significance of reduction, P
Unvaccinated in 1965-66							
0	4 113	9.4	4.8				
2-3	2 627	4.6	4.8	2.0	4.8	0.64	<0.001
Total	6 740	7.7	4.8				
Vaccinated twice in 1965-66							
0	6 654	4.7	4.6	2.0	4.7	0.49	<0.001
2-3	12 002	3.5	4.2	2.7	5.9	0.40	<0.001
Total	18 656	4.0	4.3	1.9	3.7	0.31	0.001

[a] From data for the same factories as in Table 2.

this investigation for the period February-April 1966 are summarized in Tables 6 and 7.

According to the data presented in this table, only 39.4% of the morbidity recorded among the unvaccinated workers was due to influenza virus; it therefore seems likely that the real proportion of influenza cases among all the unvaccinated workers in the factories concerned in February-April 1966 was not 10.8% but 39.4% of the latter figure, i.e., 4.3% (see Table 7). By a similar line of reasoning, the real proportion of influenza cases among the vaccinated workers may be taken as 27.5% of 3.5%, i.e., 1.06%. The serological evidence thus suggests that the index of effectiveness for the vaccine used on these workers was not 3.1 but 4.1.

Reactogenicity

The reactogenicity of the vaccines used was tested in 2436 vaccinated persons (40 to 200 persons per vaccine batch). No batch was found to exhibit reactogenicity exceeding the maximum permissible level (2% of reactions accompanied by a temperature above 37.5°C). The number of reactions with lower temperatures depended on the vaccine batch used; after the first vaccination it ranged from 6% to 19% for vaccine A2 and from 6% to 17% for vaccine B, and amounted to 11.3% among 44 persons given placebo. The second and third vaccinations resulted in only an insignificant increase in temperature in isolated cases. The number of vaccinated persons confined to bed by influenza or other ARD

TABLE 6

SEROLOGICAL DATA ON CASES OF INFLUENZA IN TWO FACTORIES [a]

Vaccination status	No. of cases	Fourfold or greater antibody rise					
		To influenza A2 virus		To influenza B virus		Total	
		No.	%	No.	%	No.	%
Vaccinated	131	21	16.0	15	11.5	36	27.5
Unvaccinated	99	19	19.2	20	20.2	39	39.4

[a] The knitted-goods and flax factories in Smolensk mentioned in Table 2. The period covered by the serological investigations was February-April 1966.

TABLE 7

EFFECTIVENESS OF VACCINATION WITH LIVE INFLUENZA VACCINE IN TWO FACTORIES, FROM MORBIDITY AND SEROLOGICAL DATA [a]

Source of incidence data	Vaccination status	No. of persons in group	Incidence (%)	Cases serologically examined (%)	Index of effectiveness of vaccine	Reduction of incidence	Mean error of reduction	Statistical significance of reduction P
Morbidity records [b]	Unvaccinated	1 883	10.8	48.8				
	Vaccinated	4 633	3.5	80.0	3.1	7.3	0.65	<0.001
Serological tests [c]	Unvaccinated	1 883	4.3	—				
	Vaccinated	4 633	1.06	—	4.1	3.2	0.38	<0.001

[a] The factories and the period of investigation concerned are the same as in Table 6.
[b] Of influenza and other ARD.
[c] Of influenza.

during the period of immunization both in 1964 and in 1965-66 did not differ significantly from the rate among unvaccinated persons, which confirmed the absence of any considerable reactogenicity.

Take rate and immunogenicity

The mean take rates of the B and A2 vaccines used by us in 1964 in persons with low antibody titres in the blood (up to 1:20) were 68.6% and 68.8% respectively; the take rate varied considerably with the series used. Vaccine B also took well in persons possessing higher homologous antibody titres in the blood, while vaccine A2 took much worse: the take rate for vaccine A2 in 155 persons examined was only 29.0%.

The immunogenicity level of these batches of the vaccine was lower than that officially prescribed (4-fold or greater rise in antibody titre in the blood in 50% of the vaccinated). In 1964-65, vaccine A2 caused a 4-fold or greater rise in antibody titre in the blood in only 23%-45% of subjects with low initial titres vaccinated 2 or 3 times, and vaccine B in 33%-45%; the average increase in antibody titre was 2.0-fold to 3.6-fold for vaccine A2 and 2.2-fold to 4.6-fold for vaccine B. The increase in antibody titre in the blood of persons vaccinated in 1964 against strain A2/England 12/64, which is antigenically similar to the viruses circulating during the 1965 epidemic, was even smaller (4-fold increase in antibody titre in the blood of 15%-35% of vaccinated persons; 1.5-fold to 2.9-fold average increase in antibody titre).

The take rate of the batches of vaccine B used for vaccination in 1965-66 was as high as 70.9%-95.8%; they also caused a 4-fold or greater rise in antibody titre in 40%-48% of vaccinated subjects, depending on the vaccine series used. The two batches of monovalent vaccine A2 tested were found to possess a lower take rate and immunogenicity: the vaccine took in 20%-43% of the vaccinated and provoked a 24.4%-37% rise in antibody titre, depending on the vaccine batch used.

Etiology

The etiology of the 1965 epidemic in Smolensk was supported by the isolation of 4 strains of influenza A2 virus from the affected subjects.

Investigation of the antigenic structure of one of these strains by cross-haemagglutination-inhibition tests revealed that it was neutralized by the antisera against old strains A2/Singapore/57 and A2/Krasnodar 101/59 only 8 to 16 times less than by antisera against homologous strains. These findings indicate that the virus circulating during the 1965 epidemic was a new variant of the influenza A2 virus, which has been confirmed by the WHO Influenza Centre in Moscow and the WHO World Influenza Centre in London. Investigation of the paired sera of patients demonstrated that of 230 influenza cases observed during the epidemic 121 were due to influenza A2 and only 15 to influenza B.

In February, March and April 1966, 3 strains of influenza A2 virus were isolated; serological evidence of infection was obtained from paired serum samples (see Table 6).

DISCUSSION

The second part of this study coincided with the spread and development of an influenza epidemic

caused by a new antigenic variant of influenza A2 virus. The observation period from February 1966 to April 1966 was essentially pre-epidemic as regards influenza. The onset of the epidemic in late March and April was well marked in three control towns—Kaluga, Vitebsk and Safonovo—but the course of the epidemic was checked by the coming of summer (see the figure above). The considerable number of cases of influenza A2 and B (30%-40% of all ARD cases) in two factories in Smolensk where serological tests were carried out provided evidence of the pre-epidemic form of the disease in Smolensk (Table 6). The considerable circulation of influenza virus among the population made it possible to reveal the effects of vaccination of about half the population in certain towns on the level of incidence.

The evidence on the age distribution of acute respiratory diseases (Table 1) indicate that large-scale vaccination against influenza had a favourable effect on the morbidity rate in a town as a whole, in view of the 1.5-fold to 3-fold reduction in morbidity in Smolensk and Jarcevo among the adult population, 53%-70% of which was vaccinated against influenza.

The form of the morbidity-time curve (rising to about half the expected value at the height of epidemic and declining gradually thereafter) was also characteristic of the development of an epidemic in towns with 40%-50% of the population vaccinated: susceptible persons were more rarely encountered by the virus in the course of its travel through the largely vaccinated population, which slowed down the dissemination of the virus during the epidemic. The reduction in the incidence of influenza among the general adult population in 1965 (1.4- to 1.5-fold) and in 1966 (1.5- to 3.0-fold) was close to that found in the limited controlled trial.

Thus, this investigation has shown that large-scale vaccination is an effective means of influenza control even under the conditions of an outbreak provoked by a new variant of the causative agent, the antigenic structure of which differs essentially from that of the vaccine strain. This is in agreement with previous observations on the existence of a limited effect of onefold vaccination with a standard vaccine of a given serological subtype (A or A1) on the morbidity rate during a pandemic wave caused by the virus of a new subtype (A1 or A2) (Smorodincev & Čalkina, 1953; Anšeles, 1953; Slepuškin, 1959). Our controlled trial of the effectiveness of 3-fold vaccination revealed a statistically significant ($P < 0.01$) reduction of 1.5 times in influenza morbidity among the vaccinated (Table 3). The excellent agreement of this result with the data obtained by comparison of recorded morbidities among vaccinated and unvaccinated workers from the same industrial units indicates that the latter method can give a reliable estimate of the effectiveness of a vaccine.

A 2-fold reduction in morbidity among persons vaccinated twice, as compared with the unvaccinated, was found after the 1965-66 vaccination, even though there was no marked influenza epidemic during the observation period. The index of effectiveness for a limited group of workers was found to be 3.1 on the basis of recorded morbidity and 4.1 from serological data, which argues for the specificity of the vaccine.

The higher effectiveness of the vaccination in 1965-66 compared with that in 1964 was probably due largely to the greater similarity of the antigenic structure of new strains introduced into the vaccine to the strains circulating in nature, and to the preponderance of influenza B virus in early 1966: the B vaccine used in 1965-66 appears to have been more effective than the A2 virus, as may be seen from Table 6. The proportion of serologically proved cases of infection with influenza B virus was only 11.4% among the vaccinated subjects as compared with 20.2% among the unvaccinated, while the incidence of serologically proved cases of influenza A2 was 16.0% among vaccinated subjects and 19.2% among unvaccinated. The lower effectiveness of the A2 vaccine might be explained by the fact that vaccinations with it were carried out only once in 1965-66 and that, as mentioned above, the vaccine was not sufficiently immunogenic.

It may be mentioned that the higher immunity conferred by vaccination in both years studied than by vaccination in 1965 only (Table 5) might be partly due to the above-mentioned difference in the effectiveness of the vaccines as well as to the effect of revaccinations. It may be seen from Table 5 that 2-fold or 3-fold vaccination in 1964 followed by vaccination in 1965-66 gave a lower morbidity rate in 1966 than vaccination in 1965-66 only, while persons vaccinated in 1964 only had about half the morbidity rate in 1966 of the unvaccinated.

The finding of post-vaccination immunity lasting 8 to 10 months after a single vaccination (Unanov, 1958), or 10 to 12 months after vaccination (Sokolov, 1954; Smorodincev & Korovin, 1961), might at first

slight seem to be in conflict with the longer-lasting post-vaccination immunity described in the present communication. This difference is probably largely due to the fact that in our case vaccinations were performed twice or three times whereas Unanov's experiments were based on a single vaccination. We are at present carrying out immunological studies in an attempt to throw light on this problem.

RÉSUMÉ

Le but principal de cette enquête était d'étudier l'efficacité du vaccin antigrippal vivant bivalent, A2-B, dans les conditions d'une campagne de vaccination portant sur la population des villes de Smolensk et de Jarcevo. En novembre et décembre 1964, 97 464 personnes, soit 40,5% de la population de Smolensk et 51% de celle de Jarcevo, ont reçu une série de trois injections. En décembre 1965 et janvier 1966, on a pratiqué deux injections: la première, d'un vaccin monovalent de type B, la seconde, d'un vaccin bivalent A2-B, préparé à partir de nouvelles souches vaccinales plus proches par leur structure antigénique des virus circulants. On a vacciné 41,3% de la population de Smolensk et 52% de celle de Jarcevo, soit au total 100 359 personnes.

Afin d'évaluer l'influence de cette immunisation sur le cours du processus épidémiologique, on a comparé les indices de morbidité générale par grippe et autres maladies aiguës des voies respiratoires, au moment des épidémies de grippe qui ont eu lieu en 1962 et 1965 et de février à avril 1966 dans les villes de Smolensk et de Jarcevo, d'une part, et, d'autre part, dans des villes témoins où l'on n'avait pas procédé à des vaccinations. En outre, on a évalué l'efficacité du vaccin en comparant la morbidité des travailleurs vaccinés et non vaccinés dans les mêmes entreprises. Parallèlement à une étude générale portant sur environ 34 000 personnes (vaccinées et témoins) en 1964-1965, on a fait une expérience contrôlée plus restreinte portant sur 4335 sujets, au cours de laquelle on a injecté soit du vaccin, soit un placebo à des groupes choisis au hasard parmi des personnes employées dans les mêmes conditions.

En janvier 1965, dans toutes les villes étudiées, survint une épidémie de grippe de type A2 qui dura près d'un mois et demi. Le virus responsable avait une structure antigénique assez différente de celle de la souche vaccinale A2/Krasnodar/101/59.

L'observation a révélé que la vaccination faite en temps opportun, en deux et trois injections, est une méthode efficace de lutte contre la grippe, même lorsque l'épidémie est provoquée par un variant nouveau dont la structure antigénique diffère de façon assez nette de celle de la souche vaccinale. Les vaccinations ont influé sur le cours du processus épidémiologique, réduisant l'incidence et entraînant une diminution de 1,4 à 1,5 fois du taux de morbidité au sein des populations vaccinées. Le rapport entre l'abaissement de la morbidité et la vaccination a été démontré. Pendant l'épidémie de 1965, la morbidité a été de 25 à 50% plus faible que pendant celle de 1962 et, de février à avril 1966, la morbidité a été 1,5 à 3 fois plus faible parmi les ouvriers et les adultes — en majorité vaccinés — tandis que la morbidité parmi les enfants des villes où la population avait été vaccinée était similaire à celle des villes témoins. En outre, les indices de l'abaissement de la morbidité générale parmi les adultes étaient très proches de l'indice, statistiquement confirmé, noté dans l'expérience contrôlée restreinte et dans l'expérience plus large, où les vaccinations en deux et trois injections se sont traduites par une morbidité 1,4 à 1,9 fois plus faible parmi les vaccinés. La comparaison des indices d'efficacité dans différentes entreprises a montré que plus la vaccination d'une collectivité est poussée, plus elle est efficace.

L'efficacité de la vaccination de 1965, malgré l'absence d'épidémie caractérisée pendant la période d'observation, correspondait à une diminution de 2 fois de la morbidité. Parmi les sujets vaccinés à deux reprises en deux ans, la diminution de la morbidité était encore plus forte, à savoir 2,7 fois. L'indice d'efficacité atteint 4 si l'on se fonde sur les données de l'enquête sérologique, ce qui témoigne de la spécificité de cet effet. L'efficacité accrue de la vaccination en 1966 est probablement due au fait que les souches vaccinales et les souches épidémiques avaient des structures antigéniques plus proches et que la majorité des cas de grippe étaient dus à un virus de type B.

L'efficacité relativement modeste de la vaccination au moment de l'épidémie de 1965 s'explique par une différence notable entre la structure antigénique de l'agent causal et celle de la souche vaccinale A2/Krasnodar/101/59. Il est donc indispensable de changer périodiquement les souches vaccinales ou de les compléter par de nouveaux variants antigéniques.

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