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VACCINATION AGAINST INFLUENZA IN POLAND, 1953-56

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SYNOPSIS

The authors describe the methods, organization and results of four large-scale trials of polyvalent, intranasal influenza vaccine conducted in Poland between 1953 and 1957. Vaccination was carried out mainly in industrial establishments, workers' and students' hostels and schools. Very few post-vaccination reactions were seen.

In these trials, the formalinized intranasal vaccine, which has the advantage of being easy to administer, gave results not greatly different from those obtained in other countries with injected vaccines or with intranasal live-virus vaccine. The inclusion in the vaccine of a large number of strains, thus giving a broad antigenic spectrum, made it possible to obviate the difficulties involved in isolating a " precursor " strain, and thus made for quicker and more abundant vaccine production before an epidemic.

The preliminary work on vaccination against influenza in Poland was begun by the State Institute of Hygiene in 1951. A test sample of formalinized vaccine, containing strain PR8 adsorbed on phosphates, and a vaccine concentrated by adsorption-elution on chicken red blood cells were prepared. The vaccines were tested first on mice by intraperitoneal or intranasal immunization and intranasal challenge, and these experiments revealed a satisfactory protective power. A group of volunteers (92 people), consisting mainly of medical students in Łódź and workers of the Institute of Hygiene, were later immunized subcutaneously with the phosphate vaccine. Investigations were carried out among a number of the people vaccinated to determine the post-vaccination increase in antibodies; the

complement-fixation test was used. A decisive increase in post-vaccination antibodies against the homologous strain was noted and to a certain degree against strain B, which was not contained in the vaccine. Another group (52 students of the medical school) were immunized with the eluate vaccine intranasally with a special sprayer; serological investigation showed a post-vaccination increase in antibodies. However, there was a lower level of antibodies in those vaccinated intranasally than in those vaccinated subcutaneously, although those immunized intranasally retained a satisfactory level for a longer period of time. Both the subcutaneous and the intranasal vaccine caused only a mild post-vaccination reaction. The epidemiological effectiveness of the vaccine could not be established as there was no epidemic at the time (Przesmycki & Walkowska).

The production of the vaccine on a large scale was begun in 1953 along with preparations for an investigation among larger groups of people.

Preparation and Testing of Vaccine

Two types of vaccine were prepared from allantoic fluid of infected chicken-embryo, in which the virus was killed with formalin: (*a*) concentrated by adsorption-elution on chicken red blood cells, (*b*) adsorded on aluminium hydroxide. The antigenic composition of the vaccine changed yearly and will be given with each experiment discussed. The vaccine was tested in the following manner:

1. Haemagglutination titre determination;

2. Haemagglutination-inhibition test with specific rat sera corresponding to the virus strain contained in the vaccine;

3. Complement-fixation test using the vaccine as antigen and standard immune sera;

4. Electron microscopy;

5. Testing the vaccine on chicken-embryo for the possible presence of live virus;

6. Testing the toxic properties of the vaccine on mice;

7. Testing for sterility in the usual manner;

8. Determining the antigenic properties of the vaccine on rats by two intraperitoneal injections of 1 ml of the vaccine given one week apart. Seven days after the second injection, the concentration of antibodies in the rat sera corresponding to the strains used for the preparation of the vaccine was determined by the haemagglutination-inhibition and complement-fixation tests;

9. Testing the final concentration of formalin.

The aluminium hydroxide vaccine was tested by methods 5-9 above.

Vaccine Administration

The vaccine was administered intranasally by a special glass spraying apparatus producing a fine suspension. The apparatus was so designed as to permit introducing into the nose a sufficiently accurate amount of the vaccine. The vaccination consisted of spraying 0.5 ml of the vaccine intranasally twice at 7-10 days' interval.

Organization of Vaccination Trials

Special groups of final-year medical students or young doctors conducted the vaccination. The groups were instructed in the methods of vaccination and the problems connected with the etiology, clinical course and epidemiology of influenza. The groups organized and carried out the vaccination and then followed through with observations of incidence among the vaccinated and an unvaccinated control group. Various industrial plants, elementary schools (children from age 8), student nurses, student hostels, large offices and stores were included in the vaccination. Because it was difficult to observe the incidence among such a large group of people (100 000 to 150 000), a number of establishments were chosen for " strict observation ". The vaccinators visited those who had fallen ill in this latter group to verify influenza on the basis of a clinical observation and to drawn up a schematic case-history of the illness. Those who had fallen ill in the remaining establishments were noted from the registers of absenteeism caused by influenza. General supervision over the vaccination trial in the various areas was ensured by the public health laboratories in the given areas.

As a result of experience, the organization of the vaccination was later amended. The division of the vaccinated group into those "strictly observed" and those " controlled on the basis of absenteeism " was given up in 1955, because the practical efficiency of this system was found to be too low relative to the amount of work required. A file system was then introduced for all workers of a given establishment—those vaccinated as well as those unvaccinated (this information being noted on each card)—and a close record kept of all who had received medical leave for clinical influenza. Every four weeks the employment figures of the factory were checked and the files amended accordingly. A statistical evaluation of the efficacy of the vaccination (during the first experiment) was carried out with the help of the Pearson coefficient. In the course of the first investigation this coefficient, calculated for the different centres, was sufficiently great, and the chances of the correlation between " vaccinated twice " and " did not fall ill " being just incidental were very small ($P<0.0001$). In the next experiments the formula for the standard error deviation was used, accepting as statistically

significant the difference in incidence greater than the double standard error deviation (D>2SE).

First Experiment

This was conducted in Łódź in 1953-54. The vaccination was basically completed during November-December 1953, and schoolchildren were already vaccinated when the influenza epidemic broke out between 11 and 19 January 1954. The observation started two weeks after the completion of the vaccination and continued to 1 May 1954.

The vaccine was prepared from the following strains:

A . . . { PR8 (London, 1934)
R (Warsaw, 1949)
Shklyaver (Moscow, 1947)

A1 . . . { Pan (Moscow, 1952)
Czechoslovakia (Bratislava, 1947)

Only the eluate vaccine, which had a haemagglutination titre of from 1 : 1280 to 1 : 5120, was used.

Vaccination was chiefly carried out in student hostels and schools.

A total of 54 172 people were vaccinated twice; 10 126 vaccinated persons and a control group of 3064 unvaccinated persons were placed

TABLE 1. VACCINATION RESULTS IN ŁÓDŹ AND KATOWICE IN FIRST EXPERIMENT

City and establishment	Vaccinated twice			Vaccinated once			Not vaccinated (control group)			Index *
	number	cases	rate (%)	number	cases	rate (%)	number	cases	rate (%)	
Łódź:										
Students' hostels	2838	42	1.47	321	8	2.59	363	23	6.33	4.3
Łódź:										
Schools vaccinated before onset of epidemic	2074	98	4.72	286	11	3.84	944	101	10.69	2.2
Łódź:										
Schools vaccinated during epidemic	719	49	6.81	340	37	10.88	305	57	18.68	2.7
Katowice:										
Workers' hostel	3548	79	2.22				1452	98	6.75	3.04

* Ratio of rate among unvaccinated to rate among vaccinated.

under " strict observation " for establishing the efficacy of the vaccination. Of those vaccinated, 86.5% showed no post-vaccination reaction, 10.1% a mild reaction, 2.8% a medium reaction, and 0.3% a strong reaction. A mild reaction was characterized by slight rhinitis without a general reaction; a medium reaction by rhinitis, sore throat, a slight headache and a temperature not exceeding 37.5°C and lasting no more than three days; and a strong reaction by an illness resembling influenza, with a typical infection of the upper respiratory tract, headache and a temperature not higher than 38°C.

Sera were taken from 308 of those vaccinated, before and 10 days after vaccination, to determine the presence of post-vaccination antibodies by the haemagglutination-inhibition and complement-fixation tests.

There was an increase of antibodies against A and A1 strains in about 65% of the sera; and despite the absence of strain B in the vaccine, there was an increase in B antibodies in 25% of the sera examined.

The epidemiological evaluation of the efficacy of this vaccination took place at a time when there was an intense country-wide influenza epidemic, during which twelve A1 strains were isolated, corresponding in all respects to the Pan strain contained in the vaccine (Przesmycki et al., 1954a). The results of the vaccination are presented in Table 1. During this experiment, a comparison was made of the incidence in the establishments where people had been vaccinated with that in similar establishments in the same city where people had not been vaccinated.

The decrease in incidence among those people vaccinated (as against the unvaccinated) was of the order of 2.2 to 4.3 times (Przesmycki et al., 1954b).

Second Experiment

The second experiment was conducted in 1954-55. Vaccination was carried out in October-November 1954, and observation of incidence lasted until 1 May 1955. A total of 145 005 people in four cities were vaccinated twice—12 446 in Warsaw, 89 510 in Łódź, 24 826 in Krakow and 18 223 in Gdańsk. The efficacy of the vaccination was evaluated in 57 086 people. The composition of the vaccine used was the following:

A . . .	Zys (Warsaw, 1953)
A1 . . .	Pan (Moscow, 1952) Ł5 (Łódź, 1954) Ł6 (Łódź, 1954)
B . . .	Kri (Moscow, 1949) Bratislava (1949)

Two methods of vaccine preparation were used: concentration by adsorption and elution on chicken red blood cells, and adsorption on aluminium hydroxide.

TABLE 2. POST-VACCINATION ANTIBODY INCREASE IN FOUR CITIES IN SECOND EXPERIMENT

City	Vaccine	Number of paired sera tested	Percentage of sera showing post-vaccination titre increase					
			A antigen		A1 antigen		B antigen	
			2-fold increase	>4-fold increase	2-fold increase	>4-fold increase	2-fold increase	>4-fold increase
Warsaw	Eluate	367	10.62	2.98	22.61	10.33	9.80	9.79
	Aluminium hydroxide	65	18.46	4.60	18.46	26.15	7.69	21.53
Łódź	Eluate	213	60.04	15.49	48.83	26.75	39.9	46.4
	Aluminium hydroxide	158	67.08	9.49	52.53	26.91	56.96	27.84
Gdańsk	Eluate	280	15.0	—	17.50	0.71	26.42	4.27
	Aluminium hydroxide	166	5.42	0.60	8.43	—	12.65	1.2
Krakow	Eluate and Aluminium hydroxide	315	35.0	8.6	33.8	9.6	33.5	6.2

The haemagglutination titre of the eluate vaccine varied from 1 : 980 to 1 : 2560. Post-vaccination reactions were observed in 5658 people. A lack of reaction after the first inoculation in the different cities was noted in 84.8%-100% and after the second inoculation in 80.4%-96.4%. After the first inoculation, mild reactions varied from 2.4% to 12.2%, medium reactions from 0 to 4.1% and strong reactions from 0 to 1.2%. After the second inoculation, mild reactions ranged from 0 to 11%, medium from 0 to 9% and severe from 0 to 2.1%. The percentages given are extreme figures; the overwhelming majority of reactions were concentrated around the lowest figures quoted. Investigation of the post-vaccination antibody increase was carried out by the complement-fixation test, which was performed on paired sera taken from 1564 people in four cities. The post-vaccination antibody increase fluctuated fairly widely in the different cities. The detailed results of this study are given in Table 2.

The epidemiological evaluation of the vaccination was conducted during a country-wide B epidemic which spread in March and April of 1955. During this epidemic, six B strains were isolated from material gathered in four cities (Przesmycki et al., 1956). These strains corresponded in antigenic structure to the B strains contained in the vaccine. The results are given in Tables 3, 4 and 5 and in Fig. 1 and 2.

TABLE 3. ESTABLISHMENTS UNDER STRICT OBSERVATION IN WARSAW, ŁÓDŹ AND GDAŃSK IN SECOND EXPERIMENT

City and establishment	Vaccinated twice (eluate)			Vaccinated twice (aluminium hydroxide)			Not vaccinated			Index *	
	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	eluate	aluminium hydroxide
Warsaw: Students' and workers' hostels	1048	27	2.58	688	26	3.77	1573	110	6.99	2.71 (+)	1.85 (+)
Warsaw: Nurses' school	194	5	2.57				69	16	23.18	9.01 (+)	
Łódź: Students' hostels	1097	66	6.02				907	49	5.40	0.89 (—)	
Łódź: Nurses' schools	366	36	9.84	120	16	13.33	129	22	17.00	1.73 (—)	1.27 (—)
Łódź: Primary schools	1741	36	2.0				402	14	3.4	1.7 (+)	
Łódź: Industrial establishments	881	20	2.27	3390	55	1.62	6510	296	4.54	2.0 (+)	2.80 (+)
Gdańsk: Students' hostels	847	18	2.12	251	1	0.40	1090	36	3.30	1.56 (—)	8.25 (+)
Gdańsk: Technical boarding schools	1458	11	0.75	830	37	4.46	1202	65	5.41	7.21 (+)	1.21 (—)
Gdańsk: Nurses' school	134	3	2.23				52	5	9.61	4.3 (—)	

*** The index is the ratio of the morbidity rate among the unvaccinated to the rate among the vaccinated. The sign (+) indicates statistical significance (D>2SE), while (—) indicates that the index is not statistically significant (D<2SE).**

TABLE 4. ESTABLISHMENTS OBSERVED ON BASIS OF ABSENTEEISM IN WARSAW, ŁÓDŹ AND GDAŃSK IN SECOND EXPERIMENT

City and establishment	Vaccinated twice (eluate)			Vaccinated twice (aluminium hydroxide)			Not vaccinated			Index *	
	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	eluate	aluminium hydroxide
Warsaw: Industrial establishments	3754	150	3.99	1344	67	4.98	5495	656	11.94	2.99 (+)	2.40 (+)
Warsaw: Primary schools	2044	169	8.27	719	99	13.77	816	189	23.16	2.80 (+)	1.68 (+)
Warsaw: Students' hostel	445	25	5.61	152	12	7.89	700	77	11.0	1.96 (+)	1.39 (—)
Gdańsk: Industrial establishments	5908	113	1.91	2706	86	3.18	5168	292	5.65	2.96 (+)	1.78 (+)
Gdańsk: Primary schools	3412	79	2.31	595	14	2.35	1099	63	5.73	2.5 (+)	2.44 (+)
Łódź: Industrial establishments	1930	46	2.38	4802	97	2.02	5480	377	6.88	2.89 (+)	3.40 (+)

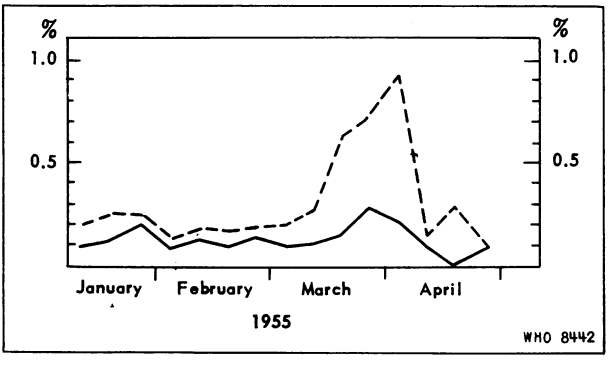
* The index is the ratio of the morbidity rate among the unvaccinated to the rate among the vaccinated. The sign (+) indicates statistical significance (D>2SE), while (—) indicates that the index is not statistically significant (D<2SE).

TABLE 5. VACCINATION RESULTS IN KRAKOW IN SECOND EXPERIMENT

Krakow	Vaccinated twice (eluate and aluminium hydroxide)			Not vaccinated			Index *
	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	
	Strict observation						
Nurses' schools	664	49	7.3	113	15	13.2	1.8 (—)
Primary schools	1701	39	2.3	669	24	3.6	1.5 (—)
Industrial establishments	2697	183	6.16	3752	307	8.18	1.3 (+)
Stores and offices	893	21	2.35	1394	154	11.05	4.8 (+)
	Observation of basis of absenteeism						
Primary schools	3529	891	25.25	326	145	44.48	1.7 (+)
Offices	2368	154	6.50	2267	268	11.22	1.8 (+)
Industrial establishments	2360	162	6.8	5963	442	7.4	1.0 (+)

* The index is the ratio of the morbidity rate among the unvaccinated to the rate among the vaccinated. The sign (+) indicates statistical significance (D>2SE), while (—) indicates that the index is not statistically significant (D<2SE).

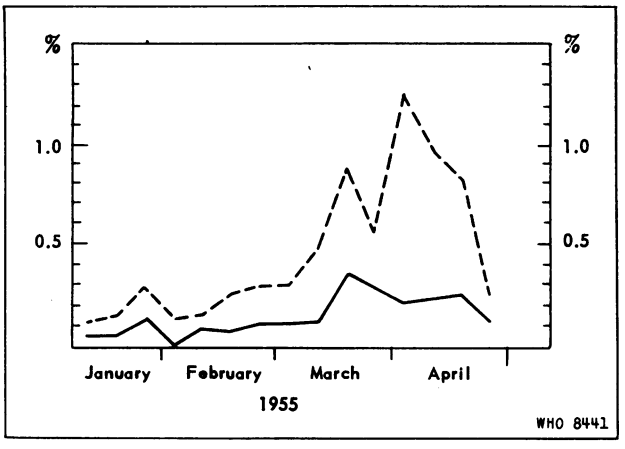
FIG. 1. INFLUENZA MORBIDITY IN 7 TEXTILE FACTORIES UNDER STRICT OBSERVATION IN ŁÓDŹ: SECOND EXPERIMENT *



* Number vaccinated: 4271; total morbidity rate: 1.7%.
Number not vaccinated: 6510; total morbidity rate: 4.5%.
Ratio: 2.6

There was, on the average, a twofold decrease of incidence among those vaccinated. A difference was noted, however, in the efficacy of the vaccination among the different cities and, to a certain degree, according to the

FIG. 2. INFLUENZA MORBIDITY IN 6 TEXTILE FACTORIES IN ŁÓDŹ OBSERVED ON BASIS OF ABSENTEEISM: SECOND EXPERIMENT *



* Number vaccinated: 6732; total morbidity rate: 2.1%.
Number not vaccinated: 5480; total morbidity rate: 6.88%.
Ratio: 3.0

type of vaccine used. Thus, in some cities, the aluminium hydroxide vaccine was the more effective.

During this second experiment, what has been called the " inner control " system was exclusively used; by this is meant that unvaccinated groups in the same establishments as the vaccinated were used as controls (Bilek et al., 1956; Przesmycki & Sawicki, 1956; Przesmycki, Sawicki & Dobrowolska, 1956; Zański & Stasik, 1956).

Third Experiment

The third experiment was conducted in 1955-56. Vaccination was completed in October-November 1955; observation continued until 1 May 1956. The total number of people vaccinated twice was 129 521 in nine cities: Warsaw, 15 224; Łódź, 43 075; Krakow, 14 992; Gdańsk, 12 765; Białystok, 5679; Wrocław, 7900; Poznań, 16 039; Katowice, 8123, and Szczecin, 5368. The composition of the vaccine was as follows:

A . . .	Zys (Warsaw, 1953)
A1 . . .	Pan (Moscow, 1952) Ł5 (Łódź, 1954))
B . . .	Kri (Moscow, 1949) B Hradec (Czechoslovakia, 1949)

The vaccine was prepared by two methods: concentration by adsorption and elution on chicken red blood cells and adsorption on aluminium hydroxide.

Changes in organization were introduced during this experiment. Vaccination was carried out by nurses in factory dispensaries or by school nurses under the supervision of doctors. The city or provincial public health laboratories supervised the vaccination through the doctors responsible. All personnel were paid from a special fund provided by the Ministry of Health. Those who fell clinically ill with influenza (among both the vaccinated and the unvaccinated) in any one factory were recorded in a special file embracing all the workers in that factory. All those who had been given medical leave for influenza were noted in the file. The weekly number of cases (among the vaccinated and unvaccinated) was noted on a special index throughout the entire period of the experiment.

1955-56 was a non-epidemic season. The results obtained in this experiment are given in Table 6.

A decrease in incidence of clinical influenza compared with the control groups during this non-epidemic season was recorded in a number of establishments. This phenomenon had not been anticipated and was not immediately understandable; it therefore required clarification through a special analysis of those who had fallen ill in all the establishments under observation. It appeared that in Warsaw, Wrocław and other localities, infections of the upper respiratory tract, identified as influenza, exceeded the non-epidemic level (Fig. 3). (In inter-epidemic periods, the official registration is usually practically nil.) Among all the establishments observed (180), there were 32 (17.7%) which during the period from November 1955 to March 1956 had an incidence of over 10% of the personnel. Of these 32 plants with high incidence there were 25 (78.1%) in which the incidence among the vaccinated showed a statistically significant reduction (see, for example, Fig. 4 and 5).

There are not sufficient data to show conclusively that the increase in incidence observed in a number of establishments was caused by virus influenza, particularly as laboratory tests were not conducted. However,

FIG. 3. INFLUENZA MORBIDITY AMONG VACCINATED PERSONS IN BIAŁYSTOK, WROCŁAW AND ŁÓDŹ: THIRD EXPERIMENT

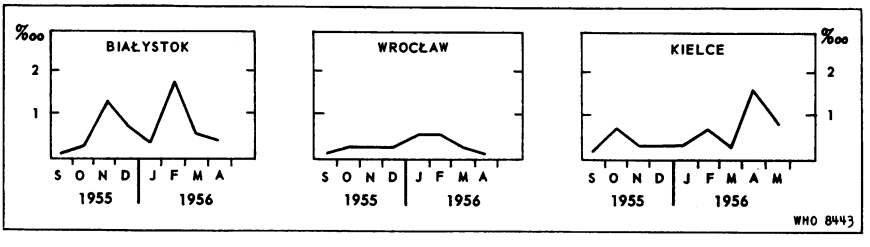


TABLE 6. VACCINATION RESULTS IN NINE CITIES IN THIRD EXPERIMENT

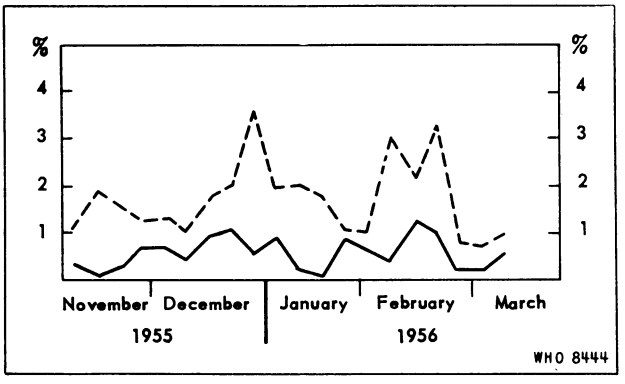
City and establishment	Vaccinated twice (eluate)			Vaccinated twice (aluminium hydroxide)			Not vaccinated			Index *	
	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	eluate	aluminium hydroxide
Białystok:											
Industrial establishments				1 411	42	2.98	1 228	62	5.05		1.69 (+)
Secondary and technical schools	1 201	24	2.00	275	2	0.73	1 025	19	1.85	0.92 (—)	2.53 (—)
Primary schools	2 459	20	0.81	423	0	0	1 601	29	1.81	2.23 (+)	
Wrocław:											
Industrial establishments	1 086	74	6.81	5 066	49	0.97	4 003	254	6.34	0.93 (—)	6.54 (+)
Metal factory **	1 748	24	1.37				2 151	101	4.69		3.42 (+)
Poznań:											
Industrial establishments	6 072	232	3.82	6 242	83	1.33	13 677	469	3.43	0.90 (—)	2.58 (+)
Offices	706	15	2.12	1 523	68	4.46	3 354	124	3.70	1.74 (+)	0.83 (—)
Primary schools	1 493	78	5.22				1 749	109	6.23	1.19 (—)	
Gdańsk:											
Industrial establishments	6 889	142	2.06	5 876	124	2.11	9 435	355	3.76	1.36 (+)	1.80 (+)

Warsaw:											
Industrial establishments	5 008	287	5.73	8 676	599	6.90	21 706	2 235	10.30	1.80 (+)	1.49 (+)
Workers' hostels				1 540	13	0.84	1 260	28	2.22		2.64 (+)
Łódź:											
Industrial establishments	17 924	1 225	6.83	25 150	1 313	5.22	50 555	4 084	8.08	1.18 (+)	1.55 (+)
Katowice:											
Industrial establishments	5 206	270	5.19	2.917	76	2.60	10 354	670	6.47	1.25 (+)	2.49 (+)
Krakow:											
Industrial establishments in city	2 541	157	6.18				2 528	231	9.14	1.48 (+)	
Industrial establishments in district	1 131	36	3.18	9 262	229	2.47	8 058	371	4.60	1.45 (+)	1.86 (+)
Primary schools	616	31	5.03	1 442	66	4.58	1 687	133	7.88	1.57 (+)	1.72 (+)
Szczecin:											
Industrial establishments	3 928	33	0.84	1 710	18	1.05	3 760	123	3.27	3.89 (+)	3.11 (+)

* The index is the ratio of the morbidity rate among the unvaccinated to the rate among the vaccinated. The sign (+) indicates statistical significance (D>2SE), while (—) indicates that the index is not statistically significant (D<2SE).

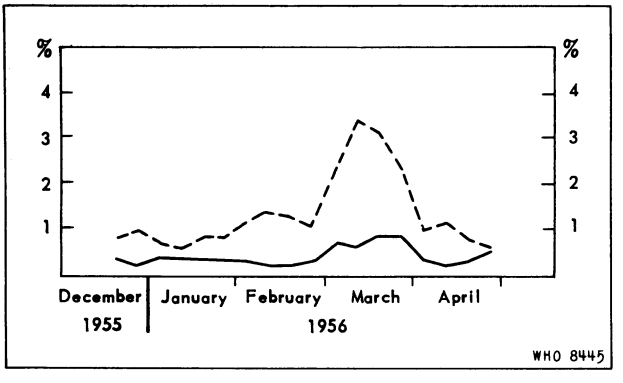
** Vaccination was performed twice in the Wrocław metal factory with both eluate and aluminium hydroxide vaccines; pooled results are shown here.

FIG. 4. INFLUENZA MORBIDITY IN A FACTORY IN WROCŁAW: THIRD EXPERIMENT *



* Number vaccinated: 476; total morbidity rate: 10.92%.
Number not vaccinated: 386; total morbidity rate: 36.53%.
Ratio: 3.34

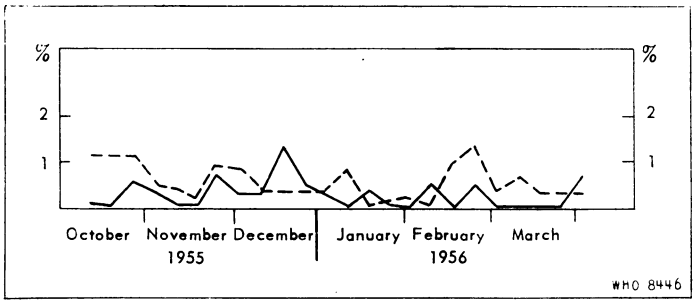
FIG. 5. INFLUENZA MORBIDITY IN WARSAW RADIO FACTORY THIRD EXPERIMENT *



Number vaccinated: 1600; total morbidity rate: 7.31%.
Number not vaccinated: 1500; total morbidity rate: 24.73%.
Ratio: 3.3

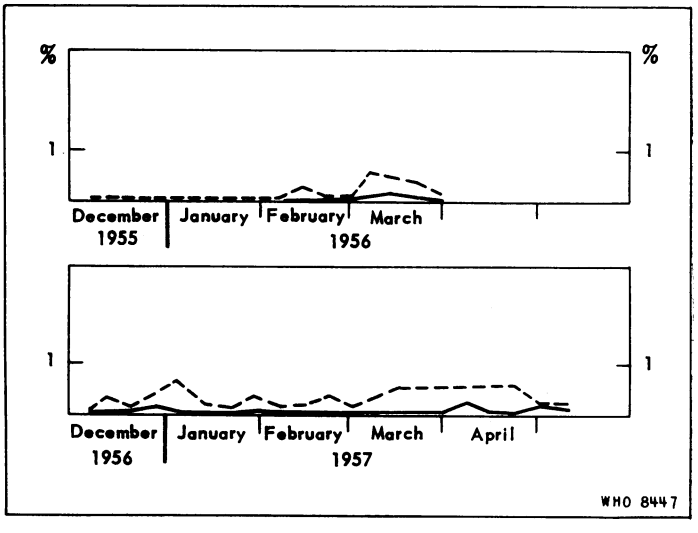
since the increase in upper respiratory infections was very marked and the clinical and epidemiological features resembled influenza very closely, one can say with some probability that the local epidemics were a sort of " precursor " of the epidemic which appeared in Poland later (March 1957) and were caused by a virus closely related to A/Netherlands/36/56. (It

FIG. 6. INFLUENZA MORBIDITY IN KRAKOW CLOTHING FACTORY: THIRD EXPERIMENT *



* Number vaccinated: 384; total morbidity rate: 6.35%.
Number not vaccinated: 265; total morbidity rate: 12.83%.
Ratio: 2

FIG. 7. INFLUENZA MORBIDITY IN WARSAW WORKERS' HOSTELS: THIRD AND FOURTH EXPERIMENTS *



* Upper graph:
Number vaccinated: 1540; total morbidity rate: 0.84%.
Number not vaccinated: 1260; total morbidity rate: 2.22%.
Ratio: 2.64
Lower graph:
Number vaccinated: 1558; total morbidity rate: 0.64%.
Number not vaccinated: 627; total morbidity rate: 5.42%.
Ratio: 9.0

should be noted that epidemics caused by this virus had already appeared in some other parts of Europe at the beginning of 1956.) A similar situation was noted in Poland in 1953-54. The mild epidemic in May 1953 was the precursor of the country-wide epidemic in January 1954 and was caused by the same strains (Sawicki, 1956a, 1956b). In relation to the situation in 1956, however, the necessary laboratory confirmation of a similar phenomenon is lacking. Nevertheless, it does seem that in a significant number of cases, the efficacy of the vaccination was in fact shown in certain factories during the local epidemics (e.g., in the radio factory in Warsaw there was an incidence of 16.4% among those unvaccinated as compared with 4.3% among those vaccinated). In a number of establishments, however, there was a statistically significant decrease of incidence among those vaccinated as compared with the controls in spite of a lack of increase of influenza registered in the establishments (Fig. 6 and 7).

It appears that the method of summarizing the cases of influenza during the entire period of observation regardless of the dynamics of incidence is unacceptable; it allows for the influence of many accidental factors, especially in the period between epidemics when the percentage of virus influenza among cases stated to be influenza is barely perceptible. The conclusion is drawn therefrom that the efficacy of vaccination can only be evaluated during a clear epidemic (even though local) in a given establishment (L. Sawicki — unpublished data).

Fourth Experiment

The fourth experiment was conducted in 1956-57. Vaccination took place in November-December 1956, and observation lasted to 1 May 1957. A total of 55 450 people in four cities were vaccinated twice: Warsaw, 12 962; Łódź, 24 219; Poznań, 6593; and Gdańsk, 11 676. The composition of the vaccine was as follows:

A . . .	Zys (Warsaw, 1953)
A1 . . .	Pan (Moscow, 1952) FM1 (London, 1947) Ł5 (Łódź, 1954)
B . . .	Kri (Moscow, 1949)

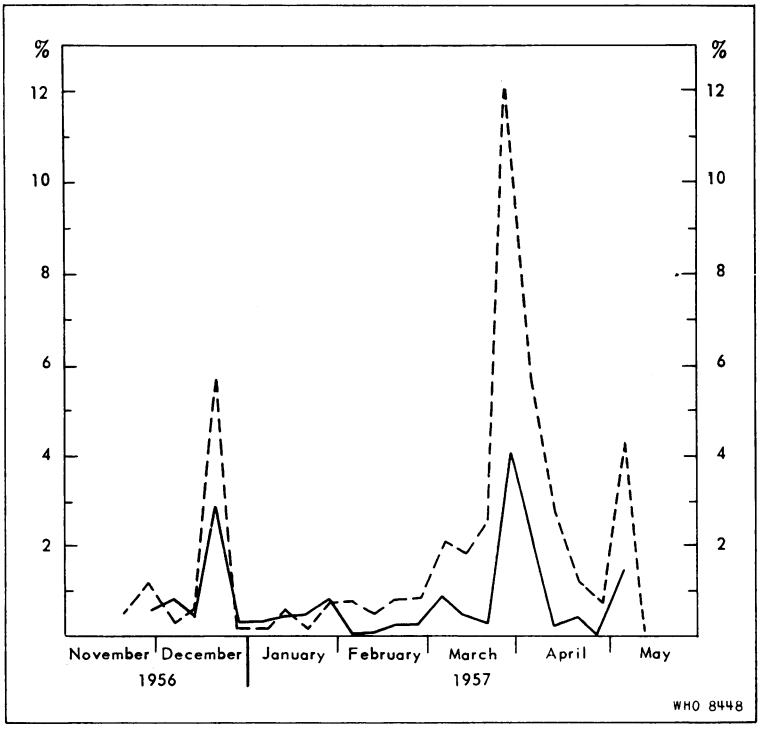
The aluminium hydroxide vaccine was used exclusively. The method of testing the vaccine was the same as in the former experiments, and the system of organization the same as in the third experiment.

The epidemiological efficacy of the vaccination was evaluated during the influenza epidemic which appeared in March-April of 1957 and was caused by a virus closely related to A/Netherlands/3/56 (L. Mietkiewicz—

unpublished data). Five strains of this kind were isolated in Poland. A statistically significant decrease of incidence among those vaccinated was seen in 40 of the 62 establishments observed. Those vaccinated in these establishments amounted to 72.2% of the total number of persons vaccinated throughout Poland. Only the incidence noted during a significant increase in the number of registrations in a given establishment was taken into consideration in evaluating the efficacy of vaccination. Incidence among those vaccinated was 1.5 to 3.4 times less than among those not vaccinated. It was shown in this experiment that the vaccine was effective even though it did not contain strain A/Netherlands/36/56. It should be mentioned, however, that in general the efficacy in this trial was less marked than in previous experiments, although it was clear-cut in some establishments (Fig. 8 and 9).

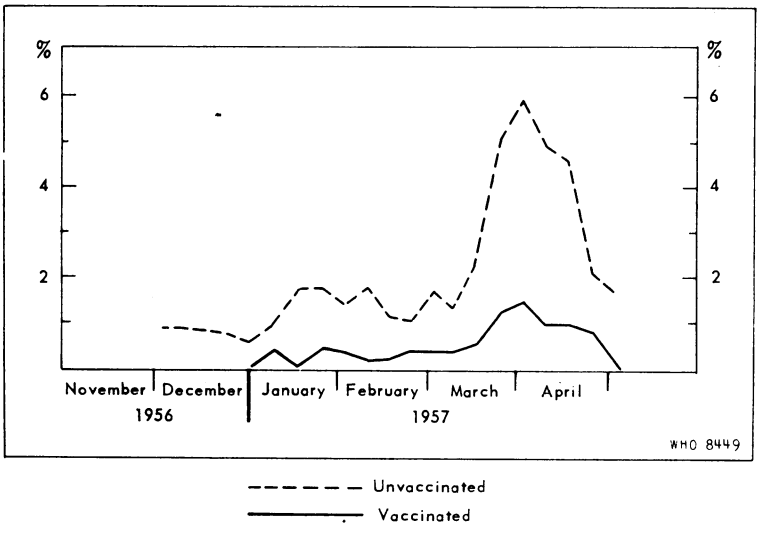
The results of vaccination are presented in Table 7.

FIG. 8. INFLUENZA MORBIDITY IN ŁÓDŹ TEXTILE FACTORY: FOURTH EXPERIMENT *



* Number vaccinated: 470; total morbidity rate: 9.36%.
Number not vaccinated: 549; total morbidity rate: 31.69%.
Ratio: 3.3

FIG. 9. INFLUENZA MORBIDITY IN WARSAW RADIO FACTORY: FOURTH EXPERIMENT *



* Number vaccinated: 658; total morbidity rate: 6.01%.
Number not vaccinated: 2304; total morbidity rate: 27.97%.
Ratio: 5.4

TABLE 7. VACCINATION RESULTS IN FOUR CITIES IN FOURTH EXPERIMENT

City and establishment	Vaccinated twice (aluminium hydroxide)			Not vaccinated			Index *
	number	cases	morbidity rate (%)	number	cases	morbidity rate (%)	
Warsaw:							
18 industrial establishments	12 962	763	5.80	23 541	3 009	12.70	2.1 (+)
Łódź:							
27 industrial establishments	24 219	2 194	9.05	22 987	3 251	14.10	1.5 (+)
Poznan:							
7 industrial establishments	6 593	465	7.05	17 505	1 807	10.32	1.4 (+)
Primary schools	1 260	188	14.92	1 524	425	27.89	1.8 (+)
Gdańsk:							
10 industrial establishments	11 676	566	4.85	8 157	624	7.60	1.5 (+)

* The index is the ratio of the morbidity rate among the unvaccinated to the rate among the vaccinated. The sign (+) indicates statistical significance (D>2SE).

Discussion

This paper presents the results of four years' investigations on the efficacy of formalinized vaccine administered intranasally. In three experiments two types of vaccine were used (eluate and aluminium hydroxide); in the fourth experiment only the aluminium hydroxide vaccine was used, since no tangible differences were noted between the two and the aluminium hydroxide vaccine is substantially cheaper and easier to prepare. The vaccine gave rise to very few post-vaccination reactions—rather less than 1%, as confirmed during the first two experiments among 12 471 persons vaccinated.

Analysing the results of vaccination, it is necessary to note that the best results were achieved during the first experiment. The epidemic broke out immediately after the completion of vaccination and in some establishments during vaccination. There was a definite reduction of incidence among children vaccinated during the epidemic. This could be interpreted by the interference phenomenon. The vaccine used during this experiment contained strain A1 (Pan), completely similar in its antigenic structure to the strain which caused the epidemic. These strains are quite similar to A/England/1/53.

The efficacy of vaccination during the second experiment was evaluated during a B epidemic of a predominantly focal character. The efficacy of vaccination varied quite extensively in the different establishments, the index of the reduction of incidence among those vaccinated ranging in general from 1.7 to 2.9 and in some establishments reaching 8.0. The strains identified during this epidemic partly corresponded to the classical Lee strain. The vaccine contained strain B/Kri/Moscow/47, very similar to Lee, and strain B/Bratislava/49.

The third experiment was most difficult to interpret since the efficacy of the vaccine was evaluated in an inter-epidemic season. A summary comparison of incidence among vaccinated and unvaccinated for the entire period of observation revealed in many establishments a statistically significant reduction of incidence among those vaccinated. A thorough analysis of incidence carried out in all establishments showed a seasonal increase of illness in some cities and industrial plants which was considered to be influenza. It is possible that during this period, which for the country as a whole was an inter-epidemic one, there were local influenza foci in which the previous vaccination was still effective and contributed to reduce the incidence. These foci may have been the precursors of the epidemic which broke out in March 1957.

In the fourth experiment a reduction of incidence among those vaccinated was achieved, of an order of from 1.5 to 3.4. The strains included in the vaccine were selected in order to achieve a broad antigenic spectrum.

The vaccine did not contain strain A/Netherlands/36/56, which was not available when the vaccine was being prepared. Perhaps the efficacy of the vaccine can be attributed to the fact that strains Pan and Ł5 (similar to A/England/1/53) included in the vaccine share some antigenic components with A/Netherlands/36/56.

In general, the efficacy of vaccination achieved by using a polyvalent, formalinized, intranasal vaccine is not much different from that obtained with influenza vaccination in other countries. The use by the Polish State Institute of Hygiene of a greater number of strains giving a broad antigenic spectrum seems to have made it possible to avoid the difficulties involved in isolating a precursor strain in order to include it in the vaccine. In practice this allowed for the production of a greater amount of vaccine before an epidemic.

It also appears that the value of the vaccine described and of the method of vaccination lies in the simplicity of application and the practically negligible post-vaccination reactions.

In order to determine the increase in post-vaccination antibodies, 2160 paired serum samples of vaccinated persons were analysed during the first and second experiments, but the results were not uniform, the antibody increase varying extensively and being different in different cities. At times differences connected with the type of vaccine were also noted. Most striking is the lack of parallel between the antigenic and protective power of the vaccine, which was revealed on an extensive scale in a number of epidemiological investigations. The possibility cannot be excluded that the immunizing mechanism of the intranasal vaccine is based to a considerable degree on local immunity phenomena of the upper respiratory tract induced by the vaccine. This hypothesis requires affirmation in a special investigation.

RÉSUMÉ

Un vaccin antigrippal, formolé et concentré, a été appliqué par voie intranasale, au cours de quatre années. à des groupes importants d'ouvriers et d'écoliers. Les résultats de ces essais, les méthodes de production, de contrôle et d'application du vaccin sont décrits dans cet article.

Les vaccins contenaient en règle générale, 5-6 souches de virus A, A1 et B. Ils étaient concentrés par adsorption-élution ou adsorbés sur hydroxyde d'aluminium, et administrés par voie intranasale deux fois, à une semaine d'intervalle, au moyen de pulvérisateurs en verre.

Le vaccin a provoqué moins de 1% de réactions vaccinales parmi 12 471 sujets vaccinés. Lors des premiers essais, 54 172 personnes ont été vaccinées deux fois. La fréquence de la grippe parmi les vaccinés, déterminée au cours d'une épidémie à virus A1, qui en 1954 a affecté l'ensemble du pays, a été réduite de façon significative (indice de réduction 2,2-4,5). Durant la deuxième expérience, au cours d'une épidémie B en 1955, on observa une diminution de moitié de la fréquence des cas déclarés parmi 145 000 personnes vaccinées, dans quatre villes. L'efficacité très nette de la troisième vaccination a été observée au cours d'une période interépidémique en 1956, dans un certain nombre

d'usines, où ont éclaté des poussées d'infections respiratoires aiguës. Ces foyers étaient probablement les précurseurs d'une épidémie causée par un virus apparenté à A/Netherlands/36/56. L'épidémie de 1957, causée par ce virus, a été l'occasion d'une quatrième expérience. Au total 55 450 personnes ont été vaccinées dans quatre villes. Le vaccin ne contenait pas le virus Netherlands/36/56, mais plusieurs autres ayant avec lui des antigènes communs. La réduction de la fréquence a été moindre que dans les précédents essais; l'indice de réduction a oscillé autour de 2.

Lors des deux premières expériences, l'accroissement du taux des anticorps a été vérifié. Il variait entre de larges limites et aucun parallélisme n'a pu être établi entre le pouvoir antigénique du vaccin et son efficacité épidémiologique.

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