Clinical and epidemiological evaluation of a live, cold-adapted influenza vaccine for 3–14-year-olds

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Reported is a study of live, cold-adapted (CA) reassortant mono-, di-, and trivalent influenza type A and B vaccines in a series of controlled clinical and epidemiological investigations involving nearly 130 000 children aged 3–15 years. The results of clinical, immunological, and morbidity investigations of the vaccinees and a control group over 6-months' follow-up indicated that the vaccines were completely attenuated by the children. Transient febrile reactions occurred in <1% of the children after vaccination, including double seronegative individuals with low antibody titres. The type A reisolates examined were genetically stable. The reassortants did not suppress each other after simultaneous inoculation of children and stimulated antibody response to influenza virus strains A1, A3, and B. The incidence of influenza-like diseases was approximately 30–40% lower among the vaccinated group than among the control group. The study demonstrates, for the first time, the efficacy of CA vaccine against infections caused by influenza B virus.

Introduction

In recent years great progress was made in the development of live, attenuated influenza vaccines. Greatest attention has been given to the development of cold-adapted (CA), attenuated reassortant vaccines, which are widely used in the Russian Federation for the immunization of children. The reassortant CA serotype A vaccines, developed at the Virology Department of the Institute of Experimental Medicine, St. Petersburg, and intended for the vaccination of children, use the donor strain A/Leningrad/134/47/57 (H2N2). This strain was prepared after 47 passages at 25 °C and has mutations in the PB2, PB, PA, NP, M2 and NS2 genes (*1*). Reassortant strains for use as vaccines contain not less than five genes from the CA donor strain that code for nonglycosylated proteins and include all the genes with *is* mutations and genes that code for the HA and NA genes of the wild-type epidemic viruses (*2*). The same principle was used to obtain influenza B virus reassortants using the CA donor strain B/USSR/69/60. Before the vaccines could be approved for general use, a series of controlled clinical and epidemiological investigations were carried out to study any reactions as well as the immunological and protective responses to them in children and in various towns of the former USSR as well as in Havana, Cuba (*3*). The results of these studies are reported here.

Materials and methods

Study population, study design and vaccines

Evaluation studies were carried out in four stages using the following commercially available live influenza vaccines: monovalent type A vaccine; divalent vaccine (type A (H1N1) and (H2N2)); divalent vaccine (type A (H1N1) and type B); trivalent vaccine (type A (H1N1), type A (H3N2) and type B). A sample of children aged 3–15 years from schools and kindergartens in St. Petersburg, Kaliningrad, Alma-Ata (now Almaty), and Havana was vaccinated. A total of 131 930 children participated in the study, as shown in Table 1. Before the children were vaccinated, their parents were advised about each study and their consent was required before any child was enrolled. The children selected had no contraindications to vaccination and were chosen from previously prepared school and kindergarten enrolment lists. Children from each school or kinder-

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Table 1: **Scheme for the clinical and epidemiological investigations of live, cold-adapted influenza vaccine**

Place of study, year	Type of vaccine	Children's age (years)	No. of vaccinees
Kaliningrad, 1986	A(H1N1)	3–6	1722
		7–14	3687
	Placebo	3–6	1723
		7–14	3836
Alma-Ata, 1987	A(H1N1) + A(H3N2)	3–6	6982
		7–14	25113
	Placebo	3–6	6721
		7–14	18164
Alma-Ata, 1989	A(H1N1) + A(H3N2)	3–6	8117
		7–14	21573
	Placebo	3–6	7524
		7–14	24345
Havana, 1990	A(H1N1) + B	3–6	288
		7–14	452
	Placebo	3–6	120
		7–14	139
Havana, 1991	A(H1N1) + A(H3N2) + B	3–6	381
		7–14	374
	Placebo	3–6	353
		7–14	316
Total	Vaccine	3–14	68689
	Placebo	3–14	63241

garten were randomly divided into groups to receive either influenza vaccine or placebo. The vaccine or placebo (physiological solution) was administered intranasally using a spray device; two doses were given (total volume 0.5 ml) at an interval of 21–28 days between doses.

Clinical and laboratory studies

Groups of 100 children who had received vaccine or placebo were examined clinically each day for 7 days by paediatricians, who recorded their temperatures and examined their skin, eyes and nasopharynx.

In order to determine whether the vaccine was innocuous, we carried out haematological (full clinical blood analysis, including counts for thrombocytes and lymphocytes), biochemical (estimates of serum C-reactive protein, as well as protein fractions, and neuraminic acid and blood urea levels), and urine analyses on 20 children from each group as follows: before vaccination; 3 days after the first dose; 1 month after the first dose; 3 days after the second dose; and 1 month after the second dose.

The IgE concentration in the blood serum of children was determined using a radioimmunological method (Phadebas test) in order to investigate any allergic reactions.

Lymphocyte function was measured using an antigen-conditioned blast-transformation.[a]

Haemagglutinin-inhibition (HI) tests were carried out to identify any changes in antibody titre. Tests for vaccine immunogenicity were performed using paired samples collected from subgroups who had been immunized before the main vaccination programme began. The antigens used were those contained in the vaccine. Standard methods for HI tests were used, including treatment of serum specimens with receptor-destroying enzymes (*4*).

Epidemiological methods were also used to estimate the safety of the vaccines, based on the analysis of somatic and infectious diseases (other than influenza and acute respiratory diseases) among the vaccinated and unvaccinated children up to 6 months after the immunizations occurred.

[a] *Report of a IUIS/WHO working group: use and abuse of laboratory tests in clinical immunology. Critical consideration of eight widely used diagnostic procedures.* WHO unpublished document, 1981.

Surveillance of influenza outbreak and data collection

Starting in mid-October, a nurse in each participating school and kindergarten began to record details of acute respiratory diseases on medical certificates. A series of specific diagnoses were used. When acute respiratory disease increased, virological surveillance (pre- and post-illness blood and nasal swabs) was started to identify influenza viruses.

The effectiveness of the vaccines was estimated by comparing the incidences of influenza and acute respiratory diseases with those among the placebo group, taking into account clinical diagnoses made on children vaccinated during influenza epidemics. These data were used to calculate the index and coefficient of effectiveness; 95% confidence intervals were also determined.

Results and discussion

Safety

Clinical examination of the children who received monovalent, di-, or trivalent vaccines indicated that they were well tolerated and that there were no serious reactions. Where reactions did occur, their incidence was low and the reactogenicity index was ≤ 0.8. Most reactions consisted of minor fever, which appeared 2–4 days after vaccination and was usually of 1–2 days' duration. No rise in systemic catarrhal or nasopharyngeal reactions was noted in vaccinated children, relative to those among the placebo group.

Children who were vaccinated in three successive years with live attenuated influenza vaccines were followed up closely. As shown in Table 2, no serious reactions occurred over the 3-year follow-up period. The incidence of upper respiratory tract, catarrhal, and systemic reactions was no greater among the children vaccinated in three successive years, compared with children who were vaccinated only once. The low vaccine reactogenicity was also confirmed independently by polyclinic physicians who were involved in the study. Children who received influenza vaccine did not suffer any more frequently from diseases than those who received placebo; the reactogenicity index was 4.0% for children who received vaccine and 7.3% for those who received placebo.

In addition to clinical examinations, the results of laboratory tests revealed no haematological abnormalities among children who received vaccines compared with those who received placebo. In rare instances where abnormalities were detected, repeat measurements were always normal.

Biochemical tests revealed the presence of C-reactive protein in two vaccinated children and two children who received placebo. Analysis of serum albumin levels in all the groups of children indicated small but significant increases in the levels of α_1 and α_2 globulins and falls at different times of the study. However, the differences were not significant between the vaccinated and placebo groups. In addition, the observed change varied greatly among individual children and could not be regarded as a stable characteristic. The urea, neuraminic acid and alanine-aminotransferase concentrations in serum

Table 2: **Frequency of febrile reactions among the study children who received live, cold-adapted influenza vaccine or placebo in three successive years**

Annual immunization period	Children's age (years)	Preparation received	*n*	No. of febrile reactions: 37.1–37.5 °C	37.6–38.5 °C	38.6 °C	Reactogenicity index
First	3–6	Vaccine	130	11 (8.4)[a]	2 (1.54)	0	0.78
		Placebo	132	11 (8.3)	1 (0.76)	0	
	7–14	Vaccine	166	9 (5.4)	1 (0.6)	0	0.6
		Placebo	168	16 (9.5)	0	0	
Second	3–6	Vaccine	39	6 (15.4)	0	0	0
		Placebo	50	5 (10.0)	0	0	
	7–14	Vaccine	70	11 (15.7)	0	0	
		Placebo	85	9 (10.5)	0	0	
Third	3–6	Vaccine	68	7 (10.3)	1 (1.5)	0	0
		Placebo	61	4 (6.6)	1 (1.6)	2 (3.3)	
	7–14	Vaccine	48	7 (14.6)	0	0	0
		Placebo	49	5 (10.2)	1 (2.0)	0	

[a] Figures in parentheses are percentages.

samples were constant during the entire period of the study, indicating that the vaccine had no detectable effects on hepatic or renal function.

Urine tests were carried out on the children at the same time as the blood examinations, and the results again were normal. Occasionally after vaccination there were traces of protein and single leukocytes present but their incidence in vaccinated groups was identical to that of the placebo group. These abnormalities always returned to normal after retesting.

Humoral responses to the following other antigens were also determined serologically during the study: parainfluenza viruses that were not present in the vaccine; and IgM and IgA in sera and nasal washings.

No decline in titres to parainfluenza viruses occurred in children administered mono- or divalent vaccine. Of 12 children of preschool age who received monovalent influenza A vaccine, six exhibited increased antibodies to parainfluenza viruses, which were probably caused by intercurrent infections. Also, there were no significant changes in the immunoglobulin concentrations of serum and nasal washings.

There was no evidence of any overall decline in the local or general immune responsiveness of children following administration of the live, attenuated influenza vaccines.

To investigate any allergies induced in the children by the vaccines, we determined the antibody levels to chicken embryo protein in both the vaccinated and unvaccinated children, since chicken embryos were used to grow the vaccine viruses. No changes were detected for children who received mono-, di-, or trivalent vaccines or for those who received placebo. Increases in the levels of antibodies to chicken proteins varied from 25% to 39%; the proportion of children who exhibited increases in their level of antibodies to the vaccine varied from 56.5% to 66.7%. A significant increase in antibody to chicken embryo proteins occurred 28 days after immunization among children who received divalent vaccine. Previous studies have shown that such an increase is of short duration and that subsequently no child exhibited allergic reactions following consumption of eggs or egg products. Further evidence for the absence of allergic reactions to immunization was provided by estimates of the IgE levels of children who received divalent vaccine or placebo. The average levels of IgE in the sera examined were in accordance with the normal physiological range (Table 3).

Virus, non-specific, cell-mediated immune responses to immunization were measured by blast transformation (Table 4). Specific rises in blast transformation activity occurred on the 7th and 21st days after the initial vaccination and on the 21st day after revaccination.

To study the effect of the influenza vaccine on the functional activity of polymorphonuclear leukocytes, we measured the following: the migratory activity of stimulated leukocytes in capillary tubes; the capacity of such cells to absorb tetrazolium salts; and the fermentative capacity of cationic lysosomal proteins in stimulated leukocytes. All these studies were carried out on blood collected from preschool-age children who had been immunized with the divalent vaccine or placebo. On the 7th day after vaccination, inhibition of leukocyte migration was the same among vaccinated and unvaccinated children. In addition, diformazan staining indicated that the cell-count of immunized children had increased by 17–24% compared with 10–15% in healthy unimmunized controls. These parameters remained the same 28 days after immunization. Also there were no significant changes in the concentration of cationic lysosomal proteins on the 7th or 28th days after immunization.

The data in Table 5 show that the incidences of common diseases among the vaccinated children were comparable with those who received placebo.

Table 3: **Concentration of IgE in the sera of children vaccinated with live, cold-adapted influenza vaccines**

Vaccine	Age of children (years)	*n*	Concentration of IgE (IU)	
			Before vaccination	28 days after vaccination
Monovalent	7–15	13	102.7 ± 37.5	105.6 ± 35.9
A(H1N1)	3–6	11	52.0 ± 21.3	43.5 ± 27.9
Bivalent	7–15	11	160.6 ± 78.8	155.0 ± 62.7
A(H1N1) + A(H3N2)	3–6	6	30.7 ± 5.8	38.5 ± 13.1
Placebo	7–15	11	61.7 ± 12.8	64.1 ± 13.9
	3–6	11	65.5 ± 15.2	64.7 ± 11.6

Table 4: **Effect on the functional action of lymphocytes of immunizing preschool children with live, cold-adapted influenza vaccines**

Antigen	Preparation	Stimulation index for period:[a] A	B	C	D
A(H1N1)	Vaccine	0.86 ± 0.11	1.69 ± 0.23	1.96 ± 0.22	1.37 ± 0.29
	Placebo	1.27 ± 0.19	1.09 ± 0.07	1.19 ± 0.09	1.12 ± 0.12
A(H3N2)	Vaccine	1.06 ± 0.09	1.80 ± 0.16	2.00 ± 0.14	1.67 ± 0.43
	Placebo	1.51 ± 0.18	1.28 ± 0.08	1.42 ± 0.08	1.05 ± 0.05

[a] A = before vaccination; B = 7 days after vaccination; C = 21 days after vaccination; and D = 7 days after revaccination.

Table 5: **Incidence of somatic and infectious diseases[a] among children up to 6 months after immunization with live, cold-adapted influenza vaccines**

Disease	First year of vaccination: No. in vaccine group (n = 1224)	No. in placebo group (n = 1191)	Second year of vaccination: No. in vaccine group (n = 220)	No. in placebo group (n = 195)
Tonsillitis	8 (0.7)[b]	20 (1.7)	1 (0.45)	0
Phlegmon, abscess	0 (0)	1 (0.1)	0	0
Furuncles	1 (0.1)	1 (0.1)	0	0
Acute intestinal infections	4 (0.3)	3 (0.3)	1 (0.45)	0
Heart diseases	1 (0.1)	0	0	0
Pneumonia	8 (0.6)	9 (0.7)	0	0
Bronchitis	49 (4.0)	66 (5.5)	5 (2.3)	6 (3.1)
Allergy	11 (1.0)	12 (1.0)	2 (0.9)	1 (0.5)
Pharyngitis, laryngitis	38 (3.1)	46 (3.9)	5 (2.3)	4 (2.1)
Kidney diseases	3 (0.2)	1 (0.1)	2 (0.9)	0
Diseases of the nervous system	1 (0.1)	0	0	0
Conjunctivitis	6 (0.5)	6 (0.5)	2 (0.9)	1 (0.5)
Other diseases	12 (1.0)	14 (1.2)	12 (5.5)	16 (8.2)
Total	151 (12.3)	184 (15.4)	30 (13.6)	28 (14.4)

[a] Other than acute respiratory diseases.
[b] Figures in parentheses are percentages.

Follow-up of the children for 6 months after vaccination showed that the indices of those diseases were the same for both observation groups. The incidences of liver and kidney diseases and of cases of pneumonia were not significantly different in the vaccinated and control groups. No allergic diseases could be detected in the vaccinated children. These studies, therefore, indicate that the vaccines used were safe and produced no detectable side-effects.

Capacity of the vaccine viruses to spread

Nasal swabs were obtained from 22 vaccinated children and 18 children who had received placebo on the first, second, third, seventh, and eighth day after the first dose. A total of 24 swabs were also obtained on days 2 and 3 after the second dose. All children were attending kindergarten. Altogether, 11 strains were isolated from the 22 children who had received a live vaccine. The vaccine virus was not isolated from any children in the placebo group, indicating that it had not spread to susceptible contacts.

Genetic stability of the vaccine strains

A total of 80 isolates from vaccinated children immunized with different CA reassortant vaccines were studied; 52 virus isolates were obtained 1–4 days

after vaccination, 16 isolates after 5–7 days, and 12 isolates after 8–9 days. All the isolated viruses had identical surface antigens to those present in the strains used to prepare monovalent vaccines, and all the isolates retained both the CA and TS phenotypes. Recombination analysis showed that the number of TS mutations in the virus isolates varied according to the time after vaccination. Viruses isolated from the children in the first few days after immunization retained the number of TS mutations that were present in the original vaccine viruses. To obtain a more precise estimate of the genetic stability of influenza A(H1N1) and A(H3N2) reassortants, we used the polymerase chain reaction (PCR) to study the mutations in all the nonsurface antigen genes of 11 isolates obtained from children on days 2, 5, and 8 after vaccination. Amplification was carried out on the c-DNA copies of those parts of the RNA genome containing mutations associated with attenuation. The results showed that all mutations associated with attenuation were retained after growth of the vaccine reassortant in the respiratory tract of children and subsequent growth in chicken embryos. The vaccine reassortants therefore, appear to be genetically highly stable.

Antigenic activity

Children immunized with the live attenuated influenza vaccines had adequate titres of haemagglutination-inhibition antibody (Table 6).

The immunogenicity of the H1N1 and H3N2 components in tri- and monovalent vaccines were the same (seroconversions: 61–63.3% for H1N1; 73.3–69.8% for H3N2). The immunogenicity of monovalent influenza B vaccine was slightly higher than for the influenza B component of trivalent vaccine (54.5% versus 43.7%). Immunization of children using live, attenuated influenza vaccine therefore induced satisfactory protective levels of antibody when the component viruses were administered as part of a mono-, di-, or trivalent preparation.

Prophylactic efficacy of vaccination

Influenza vaccine efficacy was studied over three epidemic seasons in Alma-Ata. During the 1986–87 season a divalent vaccine was used containing the H1N1 influenza virus surface antigens of the A/Brazil/1/79 strain and the H3N2 surface antigens of the A/Philippines/1/82 strain. The study was carried out during an epidemic of H1N1 virus A/Taiwan/1/86 strain; the epidemic began on 17 November 1986 and continued for 5 weeks until 21 December 1986. The maximum absenteeism among the school and preschool children occurred between 24 November and 7 December 1986. The epidemic commenced unexpectedly early in the season, coinciding with the time when the second dose of vaccine was administered. The incidence of influenza and acute respiratory dis-

Table 6: **Immunogenicity of live, attenuated mono- and polyvalent cold-adapted influenza vaccines in children aged 5–14 years with initial titres of haemagglutination-inhibition (HI) antibody <1:20**

Antigen	Preparation	No. of children	No. who seroconverted	Geometric mean HI titre (GMT)[a] I	Geometric mean HI titre (GMT)[a] II	Ratio of GMTs	No. of children with antibody titres >1:40
A/Taiwan/11/86 (H1N1)	Monovalent A(H1N1)	41	25 (61.0)[b]	8.7	31.6	3.6	21 (51.2)
	Polyvalent vaccine	49	39 (63.3)	10.4	39.4	3.8	35 (71.4)
	Placebo	45	2 (4.4)	8.8	10.2	1.1	1 (2.2)
A/Zakharpatie/354/89 (H3N2)	Monovalent A(H3N2)	45	33 (73.3)	11.5	48.9	4.3	35 (77.8)
	Polyvalent vaccine	43	30 (69.8)	10.8	49.3	4.6	36 (83.7)
	Placebo	37	2 (5.4)	14.0	16.3	1.2	4 (10.8)
B/USSR/3/87	Monovalent B	44	24 (54.5)	14.4	49.9	3.5	34 (77.3)
	Polyvalent vaccine	32	14 (43.7)	13.5	34.4	2.5	22 (68.7)
	Placebo	25	2 (8.0)	10.6	13.6	1.3	5 (20.0)

[a] I = initial titre; II = titre 3 weeks after vaccination.

Table 7: **Efficacy of live, cold-adapted influenza vaccine among children aged 3–15 years, Alma-Ata**

Years	Type of vaccine	Children's age (years)	No. of vaccinees	No. of patients with influenza-like diseases	Index (coefficient) of efficacy
	A(H1N1) + A(H3N2)	3–6	5809	1396 (24.0)[a]	1.4 (28.6)
	Placebo		5740	1946 (33.9)	
1986–87	A(H1N1) + A(H3N2)	7–14	19308	3070 (15.9)	1.4 (28.6)
	Placebo		22963	5103 (22.2)	
	A(H1N1) + A(H3N2)	3–6	8117	2540 (31.3)	1.6 (36.3)
	Placebo		7524	3564 (47.4)	
1988–89	A(H1N1) + A(H3N2)	7–14	21573	4069 (18.9)	1.6 (36.3)
	Placebo		24345	7296 (29.9)	—

[a] Figures in parentheses are percentages.

ease among the 3–6-year-old vaccines was 24.0% and 33.9% among those receiving placebo. The prophylactic efficacy index for the vaccine was 1.41 (lower limit, 1.04). The same data were obtained for 7–15-year-olds (Table 7).

A second vaccination study was carried out in Alma-Ata during the 1988–89 season where an epidemic was caused by both influenza A/Taiwan/1/86 and B/Victoria/1/87. This epidemic was characterized by average rates of illness, and affected mostly 0–14-year-olds among whom the attack rate was 60.0%. The epidemic began on 26 March 1989 and continued for 9 weeks, with the peak incidence occurring during the 4th week after onset. Although the epidemic was caused by two viruses, and the vaccine did not contain influenza B virus; good rates of protection were achieved for both preschool and school children (see Table 7).

Finally the prophylactic efficacy of three monovalent and three trivalent influenza vaccines in 5–14-year-old children in Havana, Cuba, was studied. Reassortant CA vaccine strains were prepared with the surface antigens of A/Taiwan/1/86 (H1N1) strain, A/Zakarpatie/354/89 (H3N2) strain, a variant of A/Shanghai/1/89 and B/USSR/3/87 strain, and a variant of the B/Victoria/3/87 strain. Children were immunized in November 1990 and a study to record clinical cases of influenza and of acute respiratory disease was carried out from 1 December 1990 to 31 December 1991. Episodes of acute respiratory disease occurred in Cuba in January–February and May–June 1991; a third episode began in September 1991, reached its maximum in October–November, and continued until the end of 1991. Cases of influenza and of acute respiratory disease were frequent and some children experienced several episodes of illness. These periods of acute respiratory disease were characterized by the simultaneous appearance of more than one influenza serotype in the test population. Quarterly serological records showed that the incidence of seroconversion to influenza A H3N2 and H1N1 serotypes in the period January–March 1991 was 22.7% and 20.4%, respectively; for April–June, 10.0% and 15.1%, respectively; for July–September 22.8% and 11.4%, respectively; and for October–December, 5.3% and 3.0%, respectively. Therefore, apart from the period July–September, the incidence of both serotypes of influenza virus A was similar. Over the corresponding periods the incidence of influenza B virus was 4.5%, 2.5%, 0%, and 1.7%. Monthly analysis of the incidence of influenza and of acute respiratory disease among vaccinated children aged 5–14 years (Table 8) showed that the number of children who were ill in the vaccinated group was lower than that in the control group and that the total number of diseases in the vaccinated group was also lower than in the placebo group (r = 0.001). In the control group, the total incidence of influenza and acute respiratory disease was 49.5%, while in the group administered monovalent H1N1 vaccine it was 34.2%; for the groups vaccinated with monovalent influenza A(H3N2) or influenza B vaccine the corresponding incidences were 32% and 28.3%. For the trivalent vaccine, the incidence of influenza and acute respiratory diseases was 31.5%. The coefficient of efficacy was 31.0% for A(H1N1) vaccine, 35.2% for A(H3N2), 42.8% for B, and 36.2% for trivalent vaccine.

The prophylactic efficacy of live, attenuated influenza vaccine, based on the incidence of influenza and acute respiratory disease, therefore indicates the effectiveness of all four vaccines, used either separately or in combination. In addition, our findings demonstrate, for the first time, that CA reassortant

Table 8: **Epidemiological efficacy of live, cold-attenuated reassortant mono- and polyvalent influenza vaccines for children aged 5–14 years**

Vaccine	No. of children	Total morbidity with influenza and acute respiratory disease	Index of efficacy	Coefficient of efficacy (%)
A(H1N1)	776	265 (34.2)[a]	1.45	31.0
A(H3N2)	749	240 (32.0)	1.54	35.2
B	714	202 (28.3)	1.74	42.8
Polyvaccine	755	238 (31.5)	1.57	36.3
Placebo	669	331 (49.5)	—	—

[a] Figures in parentheses are percentages.

vaccine is effective against infection caused by influenza B virus.

The efficacy of the live influenza vaccines in the study lay in the range 28.6–48.8%. This is lower than has been reported elsewhere (*5*). Perhaps, the differences arose because of an antigenic distinction between vaccine and epidemic strains as well as di- or trivalent vaccine. Vaccine efficacy also depends on the attack rates of influenza, which can vary from season to season.

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Résumé

Evaluation clinique et épidémiologique d'un vaccin antigrippal vivant adapté au froid pour les enfants de 3 à 14 ans

Cet article rend compte d'une série d'études cliniques et épidémiologiques contrôlées effectuées sur près de 130 000 enfants de 3 à 15 ans et portant sur des vaccins antigrippaux types A et B, mono-, di- et trivalents vivants, adaptés au froid et obtenus par génie génétique. Les études cliniques et immunologiques, ainsi que les enquêtes de morbidité effectuées pendant six mois sur les enfants vaccinés et sur un groupe témoin, ont conclu à une atténuation complète du vaccin. Des réactions fébriles transitoires ont été notées chez moins de 1% des enfants, parmi lesquels se trouvaient des sujets doublement séronégatifs avec des titres d'anticorps très bas. Les souches de type A isolées après vaccination se sont montrées génétiquement stables. Les vaccins ne se sont pas annulés réciproquement après inoculation simultanée et stimulaient la réponse en anticorps aux souches A1, A3 et B. L'incidence des manifestations grippales au sein du groupe vacciné a été environ 30 à 40% plus faible que dans le groupe témoin. Cette étude démontre pour la première fois l'efficacité d'un vaccin adapté au froid contre les infections dues au virus de la grippe de type B.

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