Zoster is a secondary infection due to reactivation of varicella-zoster virus (VZV), and VZV is latent in sensory ganglia after varicella [1-3]. Since loss of cell-mediated immunity to VZV is a prerequisite for development of zoster, immunization of varicella-immune persons with live attenuated varicella vaccine to boost cell-mediated immunity to VZV might be useful to prevent zoster [4, 5]. However, whether exposure to VZV in a person who has previously had varicella can subsequently result in zoster has been the subject of speculation for many years [6, 7]. It has been proposed that reexposure of varicella-immune persons to VZV may cause a suppressor immunologic effect, leading to VZV reactivation [7]. The question therefore arises: If an immunocompromised person is exposed to VZV, is their risk of developing zoster increased?

Over the past 13 years, our laboratory has collected prospective longitudinal data on the occurrence of varicella and zoster after exposure to VZV in a cohort of children with underlying acute lymphoblastic leukemia, who were immunized with live attenuated varicella vaccine [8-11]. They received 1-3 doses of varicella vaccine, and ~25% had household exposures to varicella after immunization. Detailed longitudinal data were prospectively collected that enabled us to examine these questions. We were therefore able to examine whether reexposure to VZV, either naturally or by booster doses of vaccine, protects against or predisposes to zoster.

Patients and Methods

The 511 children on whom this report is based were immunized between 1980 and 1992 by the Collaborative Varicella Vaccine Study Group [8-11]. All were receiving maintenance chemotherapy when they were immunized. Antibody titers to VZV were measured by the fluorescent antibody to membrane antigen (FAMA) method [12]. All children were seronegative (FAMA titer, <1:2) before immunization. Antibody determinations were repeated at 1- to 4-month intervals during the first few years of follow-up and thereafter at least annually. Vaccinees were followed for development of chickenpox and zoster. Events that could be identified as risk factors and other covariates were documented according to the information we received from parents and medical care providers. Two doses of vaccine were recommended in the study, but 134 children (26%) received only 1 dose. The second dose was not originally planned and was not instituted until ~1 year after the study began. Therefore, some children were given 1 dose of vaccine while others were given 2 or 3 doses. The most common adverse effect of vaccination was rash, observed in ~50% of children after the first dose of vaccine. At present, 126 of these subjects have had a household exposure to varicella, with ~85% protection against chickenpox. The children have been followed with a total of 1884 person-years of observation.

Life-table analysis together with log-rank test and generalized Wilcoxon tests were done with SAS software (SAS Institute, Cary, NC). To identify important covariates, a Cox proportional hazards model was used with BMDP software (BMDP Statistical Software, Los Angeles). Various contingency tables based on χ² analysis with continuity correction were used on a Macintosh computer with Statview software.

Results

Clinical data. Between 1980 and 1982, 113 children were vaccinated; 47% were given 1 dose and 53% were given 2 doses. Between 1983 and 1990, 398 were vaccinated; 20% were given 1 dose and 80% were given 2 doses. Of the 511, 134 had 1 dose and 377 had 2 doses.

Sixteen vaccinees (3%) developed clinical zoster. Each had seroconverted after vaccination, 15 after 1 dose and 1 after 2

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Informed consent was obtained from the patients or their parents or guardians, and human experimentation guidelines of the US Department of Health and Human Services and those of the authors' institutions were followed in the conduct of the clinical research.

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0022-1899/96/7302-0024$01.00
doses. Seven received 1 dose of vaccine, 8 received 2 doses, and 1 received 3 doses. In 2 (22%) of 9 who received >1 dose of vaccine, there was a subsequent significant increase in VZV antibody titer after the additional dose(s).

The patients ranged in age from 3 to 11 years (median, 5.4) when they developed zoster. Ten (63%) were receiving maintenance chemotherapy when they developed zoster; 4 were no longer receiving chemotherapy (stopped 3–38 months previously; mean, 14), and 2 had undergone autologous bone marrow transplantation 1 and 3 months previously. One child had two confirmed episodes of zoster 14 months apart; the rash reappeared in the same dermatome. Twelve (75%) of the 16 children with zoster were given either oral or intravenous acyclovir. In no child was the zoster considered severe.

These 16 children developed zoster an average of 1.8 years (median, 1.4) after the first dose of vaccine. The earliest time after vaccination that zoster occurred was 3 months and the latest was 4.3 years.

In 15 children, the diagnosis of zoster was proven either by virus isolation in human embryonic lung fibroblasts (3 children), by an increase in VZV FAMA antibody titer (9), by both (2), or by direct immunofluorescence of a smear of a lesion (1). Three isolates were vaccine type and 2 were wild type, as determined by analysis of viral DNA [13, 14].

Rash due to VZV occurred in 14 (88%) of 16 vaccinees who subsequently developed zoster. Twelve (75%) had a vaccine-associated rash within 1 month of vaccination, and 2 (13%), both of whom had 2 doses of vaccine, experienced breakthrough varicella. In children with a vaccine-associated rash, the rate of zoster was 5% (12/240); in those without a vaccine-associated rash, the rate was 2% (4/251) \((P = .38 by \chi^2)\). In children with a rash due to breakthrough wild type varicella, the rate of zoster was 3% (2/68); in those without wild type varicella, the rate was 3% (14/443) \((P = .38 by \chi^2)\). For vaccinees with any type of VZV rash, the rate of zoster was 5% (14/301; some vaccinees had both types of rash; see table 1); for vaccinees who never had any VZV rash, the rate of zoster was 1% (2/210) \((P = .03 by \chi^2)\).

In the 128 vaccinees who developed a leukemia relapse, there were 6 cases of zoster (4.6%). In the 383 vaccinees who did not have a relapse, there were 10 cases of zoster (2.6%) \((P = .38 by \chi^2)\). Of the 16 vaccinees who developed zoster, 6 (38%) had experienced a relapse.

The following covariates were analyzed with regard to whether they were predictive of zoster, using a Cox proportional hazards model. These variables were predicted potentially to have an influence on development of zoster. These covariates included household exposure to varicella, number of doses of vaccine, bone marrow transplantation, vaccine-associated rash, and development of varicella. The first three variables (exposure, dose, and transplantation) had a significant impact on whether zoster occurred \((P < .01)\), with household exposure having the greatest protective influence \((Z = \text{coefficient}/SE: 5.2, 3.4, \text{and} 2.1, \text{respectively})\).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1 dose</th>
<th>&gt;1 dose</th>
<th>(P (\chi^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children (%)</td>
<td>134 (26)</td>
<td>377 (74)</td>
<td>\n</td>
</tr>
<tr>
<td>No. with relapse of leukemia (%)</td>
<td>38 (28)</td>
<td>68 (18)</td>
<td>.016</td>
</tr>
</tbody>
</table>

NOTE. NS, not significant.
* 9 (7%) had both.
† 18 (5%) had both.

Zoster in children who did or did not receive second doses of varicella vaccine. Nine (56%) of 16 children who developed zoster had been given a second or third dose of varicella vaccine before their reactivation illness. Additional vaccine doses had been administered from 2.5 to 48 months (median, 16) before zoster. The rates of zoster in vaccinees who were given 1 or >1 dose of vaccine before zoster were similar for both groups (table 1).

Of the group who did not develop zoster for whom appropriate serum samples were available, 222 (54%) of 411 had a significant increase in VZV antibody titer after the second dose of vaccine. In the group who developed zoster, 2 (22%) of 9 had a significant increase in VZV antibody titer \((P = .12 by \chi^2)\).

A Kaplan-Meier life-table analysis of the immunized children is presented in figure 1. The probability of remaining free of zoster was higher in the group who received >1 dose of vaccine, by log-rank and generalized Wilcoxon tests \((P = .048 \text{ and } .026, \text{respectively})\).

Zoster in vaccinees who did or did not have a household exposure to varicella. There were 385 children with no household exposure to varicella and 126 who had household exposures. Both groups were similar with regard to age, sex, time receiving chemotherapy, number of doses of vaccine, whether they had undergone bone marrow transplantation, rate of relapse of leukemia, and past history of any VZV-related rash.

Two (13%) of the 16 children who developed zoster had prior household exposures to varicella. Each developed breakthrough varicella within 2 weeks of the household exposure. They were the only children of the 16 with zoster who had
varicella. Their zoster was due to wild type VZV and occurred 20 and 24 months after the occurrence of breakthrough varicella. The other 14 children who developed zoster had no household exposures to VZV before their zoster.

Of the children who did not develop zoster after household exposure for whom paired sera were available, significant increases (≥4-fold) in VZV antibody titer occurred in 44 (42%) of 105.

The probability of remaining free of zoster by Kaplan-Meier life-table analysis in the two groups, by log-rank and generalized Wilcoxon tests, was $P = .13$ and .09, respectively, over the entire interval of follow-up (~150 months).

**Discussion**

We compared the rate of zoster in children who had been given 1 dose of vaccine with the rate in children who had >1 dose. Since the number of doses given to these children was not determined in a randomized fashion, comparisons between the 2 groups are important to rule out the possibility of bias. Although the children were not randomized, the groups came from a very similar population of children. The only different characteristics between these groups, as shown in table 1, were the rates of breakthrough varicella and of leukemia relapse, neither of which was found to predispose to zoster in the Cox proportional hazards model. Thus, we could not identify any bias in the groups that would seem to invalidate our conclusion that additional doses of varicella vaccine protect against zoster.

We also determined whether having a household exposure to varicella influenced whether zoster developed. There was no evidence that exposure predisposed to zoster; the reverse was found. A life-table analysis did not reveal a difference in frequency of zoster between groups, although there was a trend toward less zoster in those with household exposures. The life-table analysis considered children for as long as 12 years after vaccination, with no special emphasis on the period of highest risk, those few years around the time of chemotherapy for leukemia. The more refined Cox proportional hazards model analysis, which did concentrate on this period of time, revealed that a household exposure to varicella after varicella vaccine was highly protective against zoster ($P < .01$), even more than >1 dose of vaccine. Many of these children also showed evidence of an increase in humoral immunity, reflecting immunologic boosting to VZV after the exposure.

These observations thus support the hypothesis that reexposure to VZV offers protection against zoster, as suggested by Garnett and Grenfell [15]; if the natural circulation of the wild type VZV eventually is significantly decreased by widespread use of varicella vaccine, it may be necessary to administer booster vaccine doses to adults. The live attenuated varicella vaccine was approved for immunization of varicella-susceptible healthy children and adults by the US Food and Drug Administration in March 1995. This vaccine protects against varicella. Our data further suggest that future control of zoster may be achieved not only by use of the live attenuated vaccine in varicella-susceptible persons but also by immunization of varicella-immune persons at high risk to develop zoster.

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**References**

Comparison of US Inactivated Split-Virus and Russian Live Attenuated, Cold-Adapted Trivalent Influenza Vaccines in Russian Schoolchildren


In a blinded, placebo-controlled study, the reactogenicity, immunogenicity, and clinical efficacy of single doses of US inactivated split-virus and Russian live attenuated, cold-adapted influenza vaccines were compared in 555 schoolchildren in Vologda, Russia. Serial serum samples were collected and school absenteeism was assessed. Systemic reactions were rare, but local reactions (primarily erythema at the injection site) were observed in 27% of the inactivated vaccine group, and coryza (12%) and sore throat (8%) were observed in the attenuated vaccine group. At 4 weeks after vaccination, a ≥4-fold rise in titer of hemagglutination inhibition antibody to A (H1N1), A (H3N2), and B was noted, respectively, among 78%, 88%, and 53% of children who received inactivated vaccine and among 55%, 79%, and 30% of children who received attenuated vaccine. The vaccine efficacy for preventing school absenteeism due to acute respiratory illness during the period of peak influenza activity was 56% for inactivated vaccine and 47% for attenuated vaccine.

Since 1977, a live attenuated, cold-adapted influenza vaccine made from recombinants of a master donor strain, A/Leningrad/134/17/57 (H2N2), has been widely used in mass vaccination campaigns for Russian adults [1, 2]. The donor strain had been attenuated by 17 laboratory passages in hens’ eggs at 25°C. In 1988, recombinants of this donor strain that had been further attenuated by 30 additional laboratory passages were licensed for mass vaccination of Russian children 3–14 years of age. Recently, the 17-passage donor recombinants were also approved for vaccination of Russian children. These recombinants, like those of the 47-passage donor, have few adverse reactions but are more immunogenic, generally requiring a single dose instead of the two doses required with the 47-passage viruses. In the United States, studies have shown that recombinants of master donor A/Ann Arbor/6/60 (H2N2) are safe and effective for vaccination of children [3–5]. We report a study of Russian children that compares single doses of trivalent, intramuscular, US inactivated split-virus influenza vaccine with anti-
Materials and Methods

Vaccine preparations. The following preparations were used: commercial trivalent, inactivated split-virus influenza vaccine (Wyeth-Ayerst, Philadelphia), 1990–1991 formulation, containing 15 μg each of hemagglutinin of A/Taiwan/1/86 (H1N1), A/Shanghai/16/89 (H3N2), and B/Yamagata/16/88 antigens (normal saline was used as the intramuscular placebo) and trivalent live attenuated, cold-adapted influenza vaccine (Odessa Production Company for Biological Products, Odessa, Ukraine), which was made by using the donor strains A/Leningrad/134/79/57 (H2N2) and B/ Leningrad/14/55. The wild type viruses used were A/Leningrad/ 92/89 (H1N1), A/Zakarpatie/354/89 (H3N2), and B/Yamagata/16/ 88, which were antigenically similar to those in the inactivated vaccine. Live vaccine contained 7.0–7.5 log10 EID50 of each virus per 0.5-mL dose. The intranasal placebo consisted of allantoic fluid of embryonated hens’ eggs.

Study population. Between 21 October and 1 November 1991, the Research Institute of Influenza (RII), St. Petersburg, Russia, recruited 9- to 12-year-old volunteers (grades 3–7) from two schools in Vologda, Russia. Parents or guardians chose the route of administration. After a brief history and physical examination were done, subjects were randomly assigned to receive the vaccine or placebo (within the chosen route of administration) by using a blocked randomization scheme with a vaccine-to-placebo ratio of 2:1. Persons were excluded if they had an acute illness, oral herpetic lesions, or temperature >37.0°C on the day of inoculation or a history of egg allergy or of severe reaction to previous influenza vaccination.

Interventions. A single 0.5-mL dose of inactivated vaccine or placebo was injected into the deltoid muscle with disposable, unit-dose syringes and needles. A single 0.5-mL dose of live vaccine or placebo was administered intranasally by sprayer [6]. Children enrolled during the first week (n=180) were monitored daily for 4 days after inoculation. During this week, an undetermined number of children inadvertently received their intramuscular vaccine or placebo subcutaneously. The children enrolled during the second week were monitored on the day after inoculation. Children with reactions after inoculation were monitored by pediatricians who were unaware of the child’s vaccine group until reactions and symptoms resolved. Blood specimens were collected by fingerstick on the day of inoculation and again 28 days and 5 months after inoculation. Serum samples were separated into two aliquots and stored at −20°C until tested under code.

Surveillance. Vologda schoolchildren who are absent from school for medical reasons are routinely assessed by community physicians who were not affiliated with this study. Ill children are reexamined before they return to school and are issued a letter stating the medical condition that caused their absence. This diagnosis and the dates the child was absent are recorded onto the child’s school medical card. These data covering the period 10 November 1991 through 17 March 1992 were transcribed from the medical cards at the time of serum collection 5 months after vaccination. For the purpose of this study, absenteeism due to influenza-like illness was defined as the first school absence with a physician’s diagnosis of either acute respiratory disease or influenza. The specific diagnosis of influenza refers to an acute respiratory illness that occurred during the official influenza season and is a clinical, not a virologic, diagnosis. Moreover, the clinical criteria for diagnoses were not uniform. The influenza season was defined by using morbidity and virologic surveillance data independently collected from local health clinics, schools, and work sites by the Vologda Medical Council.

Serologic testing. Aliquots of serum from each subject were tested for hemagglutination inhibition (HAI) antibody titers at the RII. Sera from about half of the children from whom 3 serial serum samples had been obtained were shipped to the Centers for Disease Control and Prevention and tested independently. Similar viruses were used in both laboratories for HAI testing [7]: A/St. Petersburg/325/88 (H1N1) and A/Vilnius/26/90(H3N2), which are antigenically similar to A/Leningrad/92/89(H1N1) and A/Zakarpatie/354/89 (H3N2) but less sensitive to nonspecific serum inhibitors, and B/Yamagata/16/88.

Statistical analysis. Ordered data were analyzed using the Wilcoxon rank sum and sign tests. Binomial data were tested with a χ2 or Fisher’s exact test. Data on the placebo groups were pooled for final analysis when no statistically significant differences between the placebo groups were noted. Seroconversion was defined as a ≥4-fold measured increase in a specific antibody titer 28 days after vaccination.

Results

Study population. A total of 555 children was enrolled and inoculated: 168 received inactivated vaccine, 87 received intramuscular placebo, 200 received live vaccine, and 100 received intranasal placebo; 245 were recruited from school 1 and 310 were recruited from school 2. The vaccine groups did not differ significantly by age, sex, school, grade attended, or proportion of children who were initially seronegative (i.e., prevaccination HAI titers of ≤10) for the 3 vaccine viruses.

Reactogenicity. The frequency of low-grade axillary fever (37.0–37.4°C) was higher for the inactivated vaccine group (9%) than for the other groups (≤3%), but this association was statistically significant only during the week of the trial when some subjects received vaccine or placebo subcutaneously. Fever (37.0–37.4°C) occurred in 5 (2.5%) of 200 children inoculated with live vaccine, 1 of 87 inoculated with intramuscular placebo, and 1 of 100 inoculated with intranasal placebo. One child inoculated with live vaccine had a documented fever between 37.5°C and 37.9°C. No other systemic reactions were significantly associated with either the inactivated or live vaccines or differed by week of trial. Local reactions were observed in 27% of the inactivated vaccine group and occurred more often during the first week (50% of vaccinees) than during the second week (11% of vaccinees). However, 93% of these reactions were limited to erythema at the site of injection. Local reaction to live vaccine consisted of coryza (12%) and sore throat (8%).

Immunogenicity. Serum antibody responses obtained by RII are summarized in table 1. Although the absolute titers
Table 1. Median serum hemagglutination inhibition antibody titers and \(\geq 4\)-fold antibody titer rises in schoolchildren in response to trivalent inactivated or live influenza vaccines, Vologda, Russia, 1991–1992.

<table>
<thead>
<tr>
<th>Vaccine component, measurement</th>
<th>Placebo ((n = 187))</th>
<th>Inactivated ((n = 168))</th>
<th>Live ((n = 200))</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H3N2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median titer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before vaccination</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>After vaccination</td>
<td>80</td>
<td>320</td>
<td>80</td>
</tr>
<tr>
<td>No. with (\geq 4)-fold rise/total (%)</td>
<td>16/172 (9) 119/157 (76) 69/176 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. seronegative* rise/total (%)</td>
<td>5/24 (21) 15/17 (88) 19/24 (79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B (H1N1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median titer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before vaccination</td>
<td>40</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>After vaccination</td>
<td>40</td>
<td>320</td>
<td>80</td>
</tr>
<tr>
<td>No. with (\geq 4)-fold rise/total (%)</td>
<td>7/171 (4) 123/157 (78) 97/176 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. seronegative* rise/total (%)</td>
<td>4/43 (9) 36/45 (80) 50/60 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median titer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before vaccination</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>After vaccination</td>
<td>20</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>No. with (\geq 4)-fold rise/total (%)</td>
<td>7/172 (4) 83/157 (53) 23/175 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. seronegative* rise/total (%)</td>
<td>6/40 (15) 23/48 (48) 14/45 (31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Prevaccination hemagglutination inhibition titer \(< 10\).

differed between laboratories because of technical differences, the major trends were similar (data not shown). A slightly higher median titer to A (H3N2) was observed in the placebo group after vaccination, but this difference was not statistically significant \((P = .9, \text{Wilcoxon signed rank test})\). All 3 serum specimens were obtained from 466 children (84%), and 2 specimens were obtained from 64 children (12%). Among vaccinees who initially demonstrated a \(\geq 4\)-fold serologic response to A (H1N1), 93% of recipients of inactivated vaccine maintained a titer of \(\geq 40\) (a conservative estimate of a protective HAI titer) compared with 82% of recipients of live vaccine. Among vaccinees who initially demonstrated a \(\geq 4\)-fold serologic response to B, 81% of recipients of inactivated vaccine maintained a titer \(\geq 40\) compared with 65% of those who received live vaccine. Similar analysis for the serologic response to A (H3N2) was complicated by the effects of a concurrent A (H3N2) epidemic.

**Vaccine efficacy.** Medical cards were reviewed for 550 (99%) of the 555 children; 94 had influenza-like illness. The Vologda Medical Council reported that an influenza A (H3N2) epidemic occurred in that city from 1 January to 2 February 1992. Estimates of vaccine efficacy against school absence due to influenza-like illness during this period were 56% for inactivated vaccine and 47% for live vaccine (table 2). Children in the placebo group were absent with influenza-like illness for a mean of 0.79 days, whereas children in the inactivated vaccine group were absent for a mean of 0.31 days during the epidemic period \((P = .05, \text{Wilcoxon rank sum test})\). Those who received the live vaccine were absent for a mean of 0.45 days \((P = .09, \text{Wilcoxon rank sum test})\). Vaccine efficacy was also estimated by using \(\geq 4\)-fold serum antibody increases to A (H3N2), the circulating virus, as tested at RI 1 month and 5 months after vaccination to confirm influenza virus infection. The vaccine efficacy against serologically confirmed influenza virus infection was 94% for inactivated vaccine and 72% for live vaccine. The vaccine efficacy against serologically confirmed absenteeism due to influenza-like illness was 100% for both vaccine preparations.

**Discussion**

This study represents not only the first time US inactivated influenza vaccines have been studied in Russia but also the first comparison of trivalent US inactivated split-virus and trivalent Russian live attenuated cold-adapted vaccines. Adverse reactions to the vaccines were minimal: erythema and edema at the site of inoculation for inactivated vaccine, particularly during the period when some vaccine was administered subcutaneously, coryza and sore throats for live vaccine, and low-grade febrile reactions for both vaccines. A high frequency of local reactions after subcutaneous administration of inactivated vaccine has been reported [8]. Both vaccine preparations were

Table 2. Efficacy of trivalent inactivated and live influenza virus vaccination against school absence due to physician-diagnosed influenza or acute respiratory disease and against \(\geq 4\)-fold rise in antibody titer to influenza A (H3N2), Vologda, Russia, 1 January to 2 February 1992.

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>Placebo ((n = 187))</th>
<th>Inactivated ((n = 168))</th>
<th>Live ((n = 200))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No./total (%)</td>
<td>18/187 (9.6) 7/167 (4.2) 10/196 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk/vaccine efficacy (%)</td>
<td>1</td>
<td>0.44*/56</td>
<td>0.53'/47</td>
</tr>
<tr>
<td>(\geq 4)-fold antibody rise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No./total (%)</td>
<td>37/163 (23) 2/147 (1) 10/160 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk/vaccine efficacy (%)</td>
<td>1</td>
<td>0.06²/94</td>
<td>0.28³/72</td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No./total (%)</td>
<td>5/161 (3) 0/146</td>
<td>0/157</td>
<td></td>
</tr>
<tr>
<td>Relative risk/vaccine efficacy (%)</td>
<td>1</td>
<td>0.004¹/100</td>
<td>0.01²/100</td>
</tr>
</tbody>
</table>

* \(P = .04\) vs. placebo (Fisher's exact test, one-tailed); \(P > .5\) vs. live vaccine (Fisher's exact test, two-tailed).

† \(P = .06\) vs. placebo (Fisher's exact test, one-tailed).

‡ \(P < .001\) vs. placebo; \(P = .03\) vs. live vaccine.

§ \(P < .001\) vs. placebo.

†† \(P < .03\) vs. placebo.
immunogenic as assessed by HAI titers; however, median titers against the 3 vaccine antigens were 2- to 4-fold higher in the inactivated vaccine group, who were also more likely to seroconvert, than in the live vaccine group. Among children who received the live vaccine and seroconverted to any of the 3 antigens, those who were initially seronegative were more likely to seroconvert. The inactivated vaccine was also more likely to produce a seroconversion to all 3 antigens (38%) than was the live vaccine (5%; data not shown).

This study is among the first to document influenza vaccine efficacy among schoolchildren on the basis of school absenteeism due to physician-diagnosed influenza-like illness. Most previous studies have calculated vaccine efficacy on the basis of postseason ≥4-fold antibody rises to the influenza antigen(s) that predominated during the previous influenza season. This approach may overestimate efficacy for inactivated vaccine because recipients of these preparations have higher postvaccination antibody titers than those who receive live vaccines. In contrast, estimates based on absenteeism due to clinical disease may underestimate the true efficacy of both vaccines because influenza virus infection cannot be readily differentiated from other viral respiratory infections by using clinical criteria.

This study and others showing the efficacy of live attenuated and inactivated influenza vaccines in preventing influenza-like illness among unvaccinated staff and children in a Russian school where children were vaccinated [9] and otitis media among children attending day care [10, 11] provide further evidence that may support a policy of more widespread influenza vaccination of children. Moreover, studies have shown that influenza virus infection causes high levels of morbidity among the very young and that school-age children often disseminate influenza in the community [12, 13]. If influenza vaccine is to be used more widely among healthy children, the annual administration of single-dose trivalent, intranasal live attenuated influenza virus vaccines, which are highly immunogenic but easy to administer and well-tolerated, may be more acceptable than an annual intramuscular injection of the currently licensed US influenza vaccine.

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References