MAJOR ARTICLE

Intranasal Influenza Vaccine in a Working Population

Pedram Sendi,[1,2] Rebecca Locher,[1] Bruno Bucheli,[3] and Manuel Battegay[1]

[1]Division of Infectious Diseases and [2]Institute for Clinical Epidemiology, Basel University Hospital, Basel, and [3]Department of Public Health, Canton Basel-Stadt, Switzerland

In the present study, we assessed the incidence of adverse events and influenza-like symptoms in a working population in Switzerland that was vaccinated against influenza. A total of 12,582 individuals of working age (<65 years old) were offered a free influenza vaccine of their choice (injectable or intranasal vaccine) in October and November 2000. Of these individuals, 1600 were vaccinated against influenza. Ninety-seven percent of the vaccine recipients chose the intranasal vaccine, and 3% chose the injectable influenza vaccine. The incidence of influenza-like symptoms and side effects was 13% and 36%, respectively. Individuals who chose the intranasal vaccine were more likely to report side effects (OR, 3.23; 95% CI, 1.29–8.08). Facial paralysis was observed in 11 patients and was the most severe adverse event associated with the intranasal influenza vaccine. As a result of these adverse events, the intranasal vaccine was removed from the market in the fall of 2001.

Influenza infections are associated with substantial morbidity and mortality and typically occur during the winter months in the northern hemisphere [1–4]. The incidence of influenza is usually highest among children [5]. However, more than any other group, elderly individuals >65 years of age and individuals with underlying chronic disease conditions are at increased risk of serious illness and death from influenza [2, 3, 6]. Vaccination is the primary measure to prevent ill health associated with infection due to the influenza virus [7]. The Centers for Disease Control and Prevention (CDC; Atlanta, GA) therefore recently recommended that persons aged ⩾65 years and adults and children with chronic disorders of the pulmonary or cardiovascular system or with chronic metabolic diseases such as diabetes mellitus should be vaccinated against influenza [8]. In addition, the CDC recommended that persons aged 50–64 years be vaccinated against influenza, because the prevalence of high-risk conditions is high in this age group [8].

However, influenza vaccination has hitherto been available only as an injectable vaccine, which may be an inconvenient route of administration for many individuals. Fear of injections and the inconvenience associated with them may prevent many potential candidates from receiving vaccination against influenza. A novel intranasal influenza vaccine (Nasaflu [Berna Biotech AG]) that is applied as a nasal spray was introduced in Switzerland in October 2000 [9, 10]. This vaccine was removed from the market in the fall of 2001 because of a possible association with facial paralysis. It should be noted that, in the meantime, another intranasal vaccine has been introduced on the market (FluMist; MedImmune Vaccines). This second intranasal vaccine is based on a live attenuated, cold-adapted influenza virus, as opposed to the inactivated, virosome-formulated subunit vaccine used in our study [11–13]. The intranasal virosomal vaccine used in our study contains as an adjuvant a heat-labile *Escherichia coli* toxin [9, 10]. The frequency and type of side effects are important for determining the long-term acceptability of the vaccine in the population. In the present study, we therefore investigated the safety of the intranasal virosomal influenza vaccine in a working population. In addition, we analyzed factors that are associated with

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Reprints or correspondence: Dr. Manuel Battegay, Div. of Infectious Diseases, University Hospital Basel, Petersgraben 4, 4031 Basel (mbattegay@uhbs.ch)

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developing side effects and influenza-like illness despite vaccination.

PATIENTS AND METHODS

Patients. A total of 12,582 employees of the Canton Basel-Stadt in Switzerland were offered the opportunity to receive vaccination against influenza in October and November 2000, before the epidemic period of 2000–2001. The Canton Basel-Stadt is one of the 26 Cantons (states) in Switzerland, and its official institutional bodies include several departments (such as the Department for Social Support and the Department of Education) in which employees of the Canton may work. Individuals who were interested in being vaccinated against influenza were asked to complete an initial questionnaire with information on their age, sex, history of allergy, pregnancy status, and presence of a chronic disease. Additional data such as household size and number of children were not obtained. Also, we did not obtain data on those individuals who were not interested in being vaccinated, because data collection started with the first questionnaire. On return of the completed first questionnaire, these individuals received a free receipt for an influenza vaccine of their choice: either injectable vaccine (e.g., Influvac [Solvay Pharma]) or intranasal spray (Nasaflu [Berna Biotech]). The intranasal spray represented an inactivated, virosome-formulated subunit vaccine. The components of the vaccines for influenza vaccination corresponded to the recommendations of the World Health Organization for the influenza season of 2000–2001 and included the following strains: A/Moscow/10/99 (H3N2)-like virus, A/New Caledonia/20/99 (H1N1)-like virus, and B/Beijing/184/93-like virus (see http://www.who.int; accessed 3 March 2004). The general recommendations for influenza vaccination in Switzerland are available at http://www.bag.admin.ch/infekt/ (accessed 5 January 2003).

Individuals who chose the nasal spray received instructions for the application of the vaccine in the respective pharmacies. The spray was administered by the vaccine recipient, with 1 spray puff in each nostril, using an atomizer. The atomizer was inserted as deeply as possible into the nostrils and then tilted upwards to the horizontal position. The spray was then released while pressing on the atomizer and breathing in through the nose. The same procedure was used to administer the second spray 1 week after administration of the first dose. Most of those individuals who chose the injectable vaccine received the injection at the Department of Public Health (Canton Basel-Stadt).

In June 2001, all individuals who had filled in the first questionnaire were sent a second questionnaire. The second questionnaire included questions asking whether the vaccinated individuals experienced influenza-like symptoms, defined as a temperature of >38°C and $\geq$2 of the following symptoms: cough, sore throat (pharyngitis), pain in the extremities (myalgia), and headache [14]. In addition, the second questionnaire elicited whether and what type of side effects were experienced after vaccination. The first reports of facial paralyses following intranasal vaccination were known at that time, and the second questionnaire therefore specifically asked whether a facial paralysis had occurred. Individuals who indicated that they had experienced serious side effects were contacted by telephone to elicit further details about the case history. Moreover, the second questionnaire elicited the type of vaccination chosen (injectable or nasal spray), whether individuals were vaccinated against influenza in the preceding winter of 1999–2000, and whether individuals had experienced influenza-like symptoms during the preceding winter.

Statistical analysis. Because the study population represents a closed cohort with a fixed follow-up period, the incidence of influenza-like symptoms despite vaccination was calculated as the proportion of individuals who experienced influenza-like symptoms in the winter of 2000–2001. The incidence of side effects following vaccination was calculated in a similar fashion.

Factors associated with developing influenza-like symptoms were first analyzed in an univariate binary logistic regression model. This model included sex, age, type of vaccine (i.e., nasal spray vs. injection), presence of a chronic disease, history of allergy, side effects after vaccination, presence of influenza-like symptoms in the winter of 1999–2000, and whether individuals were vaccinated in the winter of 1999–2000. Factors with a P value of <.1 were further analyzed in a multivariate binary logistic regression model, adjusting for age and sex.

Factors associated with side effects following vaccination were first analyzed in a univariate binary logistic regression model. This model included sex, age, type of vaccine (nasal spray vs. injection), history of allergy, presence of influenza-like symptoms during the winter of 1999–2000, and whether individuals were vaccinated during the winter of 1999–2000. Factors with a P value of <.1 were further analyzed in a multivariate binary logistic regression model, adjusting for age and sex.

The linearity assumption of the only continuous variable (i.e., age) was checked using graphical tests and restricted cubic spline functions [15]. Moreover, we checked for possible interactions in the multivariate models. All statistical analyses were conducted using the software package S-Plus, Professional Edition, version 6.1 (Insightful).

RESULTS

Patients. A total of 1623 individuals out of 12,582 potential candidates completed the first questionnaire and received a

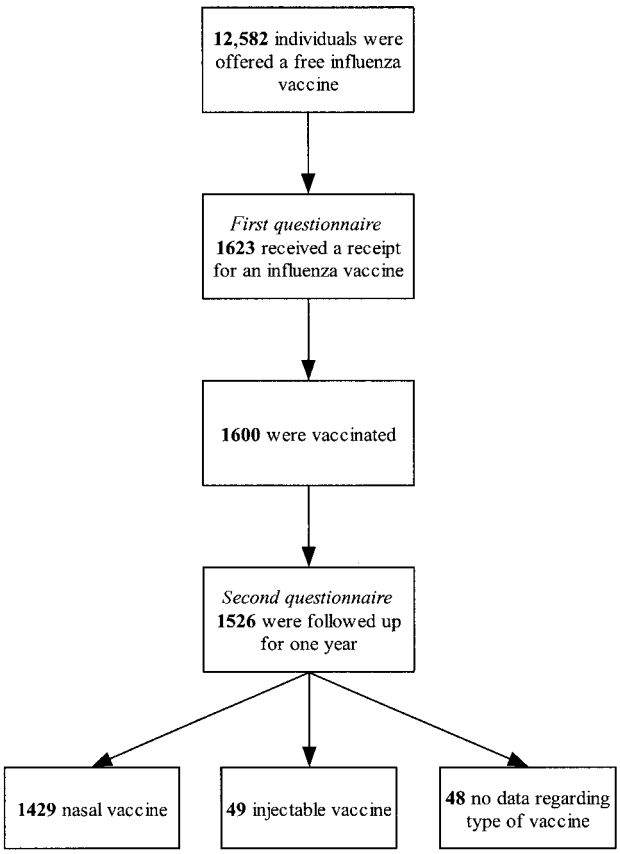

Figure 1. Flowchart indicating the number of individuals considered for and included in an intranasal influenza vaccine study in Canton Basel-Stadt, Switzerland.

prescription for a free influenza vaccine. Of these, 1600 decided to receive vaccination. A total of 1526 individuals were followed up for 1 year (i.e., completed the second questionnaire) (figure 1). Only 4.6% of those who received vaccination were lost to follow-up. The characteristics of the 1526 individuals who completed the second questionnaire are shown in table 1. The majority of these individuals (72%) were male, and the mean age was 45 years (range, 17–64 years). The vast majority (96.7%) of subjects chose the nasal spray over the injection. There was no specific algorithm for obtaining either vaccine, but the injectable vaccine was mainly recommended for elderly people and those with chronic diseases. In accordance with this recommendation, the proportion of individuals using the injectable influenza vaccine was greater among individuals with chronic diseases than among those who did not have a chronic disease (11% vs. 3%, respectively; $P < .001$). However, the mean age of those individuals who chose the injection was not significantly greater than that of those who chose the nasal spray (47 years vs. 45 years, respectively; $P = .19$). The reasons for choosing the intranasal spray are shown in table 1. A total of 57 individuals only received 1 spray and indicated that they did not use the second spray for the following reasons: side-effects (28 individuals), forgetfulness (12) or other reasons (17). Only 14% of subjects who chose the nasal spray indicated that they had chosen it because of a fear of injections, whereas 47% indicated other reasons for their choice (which were not further detailed). Twenty-nine percent of all subjects indicated that they had experienced influenza-like symptoms during the preceding winter (1999–2000). Twelve percent of subjects indicated that they were vaccinated against influenza during the preceding winter (using the injectable vaccine, as the intranasal vaccine was not available). Of these 12%, 156 (84%) chose the intranasal vaccine in 2000–2001.

Influenza-like symptoms. The incidence of influenza-like symptoms despite vaccination in the study population was 13% (198 of 1526). Factors associated with developing influenza-like symptoms are shown in table 2. In a univariate analysis, female subjects and younger subjects were more likely to develop influenza-like symptoms than were other subjects. Moreover, subjects who had experienced adverse events and subjects with a general history of allergy after vaccination were more likely than other subjects to develop influenza-like symptoms. Subjects who had experienced influenza-like symptoms in the preceding year were also more likely than other subjects to develop influenza-like symptoms. In a multivariate analysis, accounting for the joint effect of the main predictors and adjusted for age and sex, only the presence of side effects after vaccination and the history of influenza-like symptoms in the preceding year were associated with an increased risk of developing influenza-like symptoms.

Side effects. The incidence of side effects following vaccination was 36% (545 of 1526 subjects) in the study population. The side effects experienced by the vaccinated individuals are shown in table 3. Individuals who received the nasal spray could experience side effects twice, because the spray was administered twice $\geq$1 week apart. Sneezing and/or runny nose were the most common side effects after vaccination, followed by fatigue and arthralgia and/or myalgia.

Factors associated with developing side effects following vaccination are shown in table 4. In a univariate analysis, females and younger individuals were more likely to report side effects. Side effects were more frequent when the nasal spray was used, as opposed to when the injectable vaccine was used (OR, 3.23; 95% CI, 1.29–8.08). Individuals with a general history of allergy and individuals who had experienced influenza-like symptoms during the preceding winter were more likely to report side effects. Moreover, people vaccinated against influenza during the preceding winter were less likely to report side effects. In a multivariate analysis adjusted for age and sex, the direction of the ORs remained the same, with statistical significance for all independent variables other than having experienced influ-

Table 1. Characteristics of 1526 subjects vaccinated against influenza in Canton Basel-Stadt, Switzerland, winter 2000–2001.

Characteristic	Value
Female sex	425 (28)
Age, mean years ± SD	44.9 ± 10.4
History of allergy	262 (17)
Presence of chronic disease	89 (6)
Developed influenza-like symptoms	198 (13)
No prior influenza vaccination	1137 (75)
Type of vaccination[a]	
Injection	49 (3.3)
Nasal spray	1429 (96.7)
Reason for choosing nasal spray[b]	
Fear of injection	203 (14)
Less-inconvenient side effects	234 (16)
Increased efficacy	325 (23)
Other	667 (47)
History of influenza-like symptoms during winter 1999–2000	440 (29)
Vaccinated against influenza during winter 1999–2000	186 (12)

NOTE. Data are no. (%) of subjects, unless otherwise indicated.

[a] Data are missing for 48 subjects.

[b] Data are for 1429 individuals who received nasal spray vaccination.

enza-like symptoms during the preceding winter (1999–2000) (table 4).

The most severe side effect was facial paralysis. Four individuals experienced a facial paralysis after administration of the first spray of the nasal influenza vaccine. After administration of the second spray, there were 15 reported cases of facial paralysis. These cases included those of 3 of the 4 patients who experienced a facial paralysis after administration of the first nasal spray, resulting in a total of 12 patients who indicated that they had developed a facial paralysis. The diagnoses were based on patient history and clinical examinations. In 4 patients, a CT scan or MRI of the head was performed (none of which revealed any pathological findings). In 1 patient, trigeminus neuropathia was the most likely diagnosis; however, the facial nerve may have been affected as well. Therefore, there were actually 11 patients (8 male and 3 female) who experienced a unilateral facial paralysis after application of the nasal spray vaccine. The facial paralysis was on the right side in 6 patients, on the left side in 4 patients, and 1 patient could not indicate exactly on which side of the face the paralysis was located. The mean age (±SD) of the patients was 41 ± 14 years (range, 24–69 years). The mean period between administration of the most recent spray and the occurrence of a facial paralysis was 20 days (range, 3–43 days). The mean duration of the reversible facial paralyses was 26 days (range, 1.5–60 days). Within the study period, one 52-year-old patient indicated that the symptoms were not completely reversible. Because of a possible association with facial paralysis, the nasal vaccine was removed from the market in the fall of 2001.

DISCUSSION

In this study, we have shown that the majority (87%) of subjects in the working population do not wish to be vaccinated against influenza and that, among those who wish to be vaccinated,

Table 2. Factors associated with developing influenza-like symptoms in Canton Basel-Stadt, Switzerland, winter 2000–2001.

Analysis, risk factor	OR (95% CI)	*P*
Univariate analysis		
Sex, female/male	1.50 (1.08–2.07)	.015
Age, by decade	0.66 (0.57–0.76)	<.001
Vaccination method, nasal spray/injection	0.52 (0.26–1.02)	.058
Influenza-like symptoms in winter 1999–2000	2.72 (1.98–3.75)	<.001
Vaccination against influenza in winter 1999–2000	0.78 (0.48–1.26)	.312
Side effects after vaccination in 2000–2001	2.52 (1.82–3.45)	<.001
Chronic disease	1.38 (0.77–2.47)	.274
History of allergy	1.65 (1.15–2.36)	.006
Multivariate analysis		
Sex, female/male	1.02 (0.69–1.53)	.896
Age, by decade	0.69 (0.58–0.83)	<.001
Vaccination method, nasal spray/injection	0.52 (0.18–1.43)	.203
Side effects after vaccination in 2000–2001	2.24 (1.54–3.26)	<.001
History of allergy	1.28 (0.82–1.98)	.274
Influenza-like symptoms in winter 1999–2000	2.22 (1.53–3.19)	<.001

Table 3. Reported side effects in individuals who were vaccinated against influenza in Canton Basel-Stadt, Switzerland, winter 2000–2001.

	No. of patients reporting side effect after vaccination, by vaccination method		
		Nasal spray, by dose	
Side effect	Injection	First	Second
Sneezing and/or runny nose	8	428	388
Coughing	3	74	93
Arthralgia and/or myalgia	6	132	135
Malaise and diarrhea	2	36	29
Fatigue	5	143	134
Temperature of >38°C	1	20	24
Herpes	1	16	17
Facial paralysis[a]	…	4	11
Pain at the side of injection	3	…	…
Skin irritation at the side of injection	3	…	…
Other	1	88	99

NOTE. Multiple side effects per patient are possible; total number of individuals with side effects is 545.

[a] Three patients with facial paralysis after the first spray also reported facial paralysis after the second spray. In 1 patient, trigeminus neuropathia was the most likely diagnosis; however, the facial nerve may also have been affected. Therefore, there were a total of 11 patients who experienced a definite facial paralysis after application of the nasal spray vaccine.

the nasal spray is the preferred route of administration for 97%. We have also shown that side effects following vaccination occurred in 36% of vaccine recipients, that side effects were more frequent in subjects who received the intranasal spray, and that the intranasal vaccine may be associated with a unilateral, mostly reversible facial paralysis.

The majority of the working population does not wish to be vaccinated against influenza, and among those who wish to be vaccinated, the nasal spray is preferred. Only 1623 individuals out of the 12,582 persons who were offered a free influenza vaccine were interested in being vaccinated against influenza, and 1600 (12.7%) actually received vaccination. This figure is somewhat greater than the coverage rate of 8.2% in a French working population reported by Millot et al. [16]. However, among individuals at risk for serious illness for whom vaccination has been recommended in recent guidelines, higher coverage rates have been reported. For example, Kamal et al. [17] reported an immunization rate of 66.7% among individuals >65 years of age, and in a similar study by Dannetun et al. [18], a coverage rate of 30% in the same age group has been estimated. The high coverage rate in our working population may be due to the fact that a new intranasal influenza vaccine was available, which is considered by most individuals to have a more convenient route of administration than an injectable vaccine. This argument is also in line with the fact that a striking 97% of our subjects preferred the intranasal vaccine, compared with only 3% who chose the injectable vaccine. In our analysis, experiencing side effects following vaccination and having influenza-like illness during the preceding influenza season were associated with a greater risk of experiencing influenza-like symptoms during the winter of 2000–2001. This suggests that these individuals may be more susceptible to influenza infection than other individuals despite having received vaccination. Alternatively, one may speculate that the living conditions of these individuals might be different from those of other subjects and that those conditions put them at greater risk of influenza infection.

Side effects following vaccination occurred in 36% of vaccine recipients, side effects were more frequent among subjects who received the intranasal spray, and the intranasal vaccine may be associated with a unilateral reversible facial paralysis. The side effects following vaccination have been reported previously [9, 10]. In a previous study, the rate of adverse reactions following intranasal vaccination was ~25%–30% [9]. This included local and systemic responses such as runny nose, sneezing, headache, malaise, and arthralgias [9]. The corresponding figures in our study were similar, and the overall incidence of side effects was 36%. However, in 11 patients who were vaccinated with the intranasal vaccine, a facial paralysis was reported, and 1 case of trigeminus neuropathia was described. This corresponds to an incidence of 0.7% (11 of 1526 subjects), which is higher than the spontaneous incidence of 0.02%–0.04% reported in the literature [19, 20]. The reversibility of the facial paralysis was documented in all but 1 patient. Because of a possible association with facial paralysis, the intranasal influenza vaccine was removed from the market in the fall of 2001. It should be emphasized that this adverse event was not known at the time that the intranasal vaccine was introduced. Moreover, the time lag between administration of the intranasal spray and the occurrence of a facial paralysis ranged from 3–43 days, suggesting that further exploration is needed to determine the nature of this possible association. It is also not clear whether facial paralysis was the result of a local immune reaction or was caused by the intranasal vaccine itself. One may speculate that the adjuvant heat-labile toxin may have induced these adverse events. It should be mentioned that these side effects have not been reported in association with another intranasal vaccine (FluMist [MedImmune Vaccines]) that is based on a live attenuated, cold-adapted influenza virus. However, this alternative intranasal vaccine is not recommended for individuals of >50 years of age or for patients with chronic conditions.

In our study, most side effects were mild, as indicated in table 3. Nonetheless, individuals who chose the intranasal vaccine were more likely than others to develop side effects fol-

Table 4. Factors associated with developing side effects following vaccination against influenza in Canton Basel-Stadt, Switzerland, winter 2000–2001.

Analysis, risk factor	OR (95% CI)	*P*
Univariate analysis		
Sex, female/male	1.79 (1.41–2.29)	<.001
Age, by decade	0.73 (0.66–0.81)	<.001
Vaccination method, nasal spray/injection	2.28 (1.12–4.65)	.024
Influenza-like symptoms in winter 1999–2000	1.28 (1.00–1.62)	.046
Vaccination against influenza in winter 1999–2000	0.62 (0.44–0.88)	.008
History of allergy	1.68 (1.26–2.23)	<.001
Multivariate analysis		
Sex, female/male	1.83 (1.39–2.42)	<.001
Age, by decade	0.75 (0.66–0.85)	<.001
Vaccination method, nasal spray/injection	3.23 (1.29–8.08)	.012
Influenza-like symptoms in winter 1999–2000	1.18 (0.90–1.55)	.221
Vaccination against influenza in winter 1999–2000	0.63 (0.43–0.93)	.022
History of allergy	1.49 (1.07–2.06)	.018

lowing vaccination (OR, 3.23; 95% CI, 1.29–8.08). This is not surprising, because the intranasal spray causes a local reaction, which is in line with our finding that runny nose and sneezing were the most frequent transient adverse reactions. Females were more likely than males to report side effects. In addition, individuals with a known history of allergy and individuals who were vaccinated against influenza during the preceding influenza season were more likely than others to report side effects. This suggests an altered immune response in these individuals to the vaccine content.

Our study has several limitations. First, most individuals who were offered a free vaccine decided not to receive vaccination. The reason for this decision was not elicited, because only those individuals who were interested in receiving vaccination actually completed the first questionnaire. It may well be that the majority of the younger working population were aware of the less-serious consequences of influenza in healthy adults and, therefore, prefered not to receive vaccine. However, a more comprehensive study would be needed to elicit the preferences of those who did not wish to receive vaccination. Second, self-selection of individuals into the 2 treatment groups may have biased the estimate of the OR. Third, we used influenza-like illness as the endpoint, and influenza infection was not virologically confirmed. However, virological influenza diagnostic tests are not commonly performed in general practice, and clinical diagnoses based on symptoms are more in line with a real-world setting. Another limitation is that subjects may not have recalled all symptoms when asked in June 2001 (i.e., there may have been a recall bias). However, we believe that the population was rather sensitized to vaccine-related side effects and to whether influenza-like symptoms occurred after vaccination.

In conclusion, most working adults do not wish to be vaccinated against influenza. Among those who do wish to be vaccinated, the intranasal spray was the most-frequently preferred route of administration. However, because of a possible association with facial paralysis, the Swiss intranasal vaccine was removed from the market in the fall of 2001. A recently published study also suggests a strong association between this inactivated intranasal influenza vaccine and Bell palsy [21].

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