

## Comparison of adverse reactions to whole-virion and split-virion influenza vaccines in hospital personnel

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**Objective:** To compare the adverse effects, particularly generalized aching, of a trivalent, inactivated whole-virion vaccine (WVV) and split-virion vaccine (SVV) for influenza in hospital personnel.

**Design:** Recipient-blinded study; first-time vaccinees were randomly assigned to receive either of the vaccines from one manufacturer in the 1989-90 influenza season. Subjects were asked to complete a symptom questionnaire during the 48 hours after immunization.

**Setting:** Annual influenza program for staff of a tertiary care children's hospital.

**Participants:** Volunteers were sought among approximately 2200 members of the hospital staff. Of the 358 vaccinated for the first time, 333 (93%) returned the questionnaire.

**Results:** During the 48 hours after vaccination 13% of the SVV recipients reported generalized aching, as compared with 26% of the WVV recipients ( $p < 0.01$ ). Also, the SVV group reported fewer visible local reactions and more transient arm soreness, but the actual differences between the two groups were small. The occurrence of mild symptoms was equally common in the two groups (local reactions in at least 70% of cases, systemic reactions in at least 33%). In each group 1% of the subjects reported missing work because of the vaccination.

**Conclusions:** The use of SVV reduces the rate of the most objectionable of the common adverse effects of influenza vaccination. Therefore, as with children, it might be more acceptable to health care workers than the current use of WVV.

**Objectif :** Comparer les effets indésirables, en particulier les courbatures, d'un vaccin trivalent, inactivé et à virus entier (VVE) et d'un vaccin trivalent, inactivé et à virus sous-unitaire (VSU) contre la grippe chez le personnel hospitalier.

**Conception :** Étude à l'insu; les personnes vaccinées pour la première fois ont été désignées au hasard pour recevoir un de ces deux vaccins créés par le même fabricant au cours de la saison grippale de 1989-1990. Les sujets devaient remplir un questionnaire sur les symptômes au cours des 48 heures suivant l'immunisation.

**Contexte :** Programme annuel de vaccination antigrippale à l'intention du personnel d'un hôpital pédiatrique de soins tertiaires.

**Participants :** Parmi les quelque 2 200 employés de l'hôpital, on a demandé des volontaires. Des 358 personnes vaccinées pour la première fois, 333 (93 %) ont répondu au questionnaire.

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**Résultats :** Dans les 48 heures suivant la vaccination, 13 % des employés ayant reçu le VSU ont signalé des courbatures, par comparaison à 26 % de ceux qui ont reçu le VVE ( $p < 0,01$ ). De plus, le groupe VSU a signalé moins de réactions locales visibles et plus de douleurs passagères au bras, mais la différence nette entre les deux groupes était faible. La fréquence des symptômes bénins était égale dans les deux groupes (réactions locales dans au moins 70 % des cas, réactions généralisées dans au moins 33 % des cas). Dans chaque groupe, 1 % des sujets a signalé s'être absenté du travail en raison de la vaccination.

**Conclusions :** L'utilisation du VSU réduit le nombre des effets indésirables et fréquents les plus graves de la vaccination antigrippale. Par conséquent, comme chez les enfants, ce vaccin pourrait être plus acceptable au personnel soignant que l'utilisation actuelle du VVE.

Influenza continues to be a significant cause of illness and death in certain patients, especially those with underlying heart, lung or other chronic disorders. Hospital personnel have been identified as an important source of influenza for patients.<sup>1</sup> Advisory groups in Canada<sup>2</sup> and the United States<sup>3</sup> have recommended that hospital personnel who work with people at high risk for influenza complications be vaccinated annually to reduce the risk of nosocomial infections.

Influenza immunization programs for hospital workers have not met wide acceptance, and only a few reports of their success are available.<sup>4-6</sup> Fear of adverse reactions has been identified as a limiting factor.<sup>4</sup> A previous study in our institution<sup>7</sup> revealed an unexpectedly high rate of minor adverse reactions to the inactivated, trivalent whole-virion vaccine (WVV), which is currently recommended for use in adults in Canada.<sup>2</sup> To minimize the adverse effects would be a step toward increasing the acceptability of programs for health care workers.

We report a randomized controlled study of adverse reactions to WVV and split-virion vaccine (SVV) in hospital workers receiving influenza vaccine for the first time. We wanted to determine whether the SVV would result in fewer reactions, especially generalized aching and myalgia, in this group of young, healthy people, as it has among children.<sup>2,3</sup>

## Methods

Inactivated, trivalent influenza vaccines prepared for the 1989-90 season were used. The WVV was purchased from and the SVV donated by Connaught Laboratories Limited, Willowdale, Ont. Each preparation was from a single manufacturing lot. The SVV preparation contained virions disrupted through ether treatment of whole-virion preparations but was compositionally identical to the WVV preparation.

The vaccines were given during the last week of September and the first 2 weeks of October in 1989 at special clinics held in a convenient location in British Columbia's Children's Hospital, Vancouver.

The program was preceded by several weeks of intense promotional activities, including individual recruitment letters, information meetings and posters.

All of the hospital workers were invited to participate in the study. Pregnancy and allergy to eggs or other vaccine components were the exclusion criteria. Informed written consent was obtained from each participant. The study was approved by the Ethics Committee of the University of British Columbia. Participants were informed of the rates of local (68%) and systemic reactions (20%) to WVV observed in a previous study at the hospital,<sup>7</sup> which were higher than the rates cited in the product monographs. In the recruitment letter, we suggested that participants receive the vaccine at the end of their work shifts or before scheduled days off if convenient. Subjects were advised to take acetaminophen if they felt ill after vaccination.

Volunteers who had not previously received influenza vaccine were randomly assigned to receive either the WVV or the SVV. The treatment assignments were determined from a serial listing based on randomly distributed numbers in balanced blocks of 20. Nurses giving the vaccines were not blinded but played no other role in the study. An assistant assigned numbers to the subjects and verified that the subjects were blinded to the treatment given.

Volunteers who had received influenza vaccine in any previous season were assigned "routine" vaccination with WVV but were not told the nature of the preparation; data from this group will be presented only briefly. They were excluded from the controlled study because available evidence indicates that people with more experience with influenza viral antigens are at a lower risk than others for systemic adverse effects.<sup>8</sup>

The vaccines were stored as recommended by the manufacturer. All vaccines were injected into the deltoid muscle by two experienced nurses of the Employee Health Unit. Each subject was given a symptom questionnaire and asked to record and grade any local symptoms (soreness, redness and swelling) and systemic symptoms (e.g., fever, chills, generalized aching, tiredness and headache) over the

next 48 hours. Subjects were also asked to record any use of analgesic medications or work loss and to provide an overall rating of any adverse experiences. Completed forms were collected in a special drop-off box in the hospital lobby or were returned by hospital mail. Reminders were sent to those who failed to submit a report within 1 week after vaccination.

Data were gathered by staff members of the Vaccine Evaluation Center, Vancouver. The data entry technician was unaware of the premise of the study and worked off site. Quality assurance measures included independent verification of data entry for 50% of the data files. Statistical significance of differences between proportions was determined with Fisher's exact test. A one-sided test was used because we expected a difference only in the direction of fewer adverse reactions with SVV.

## Results

Of about 2200 staff members invited to participate 558 (25%) were vaccinated. A total of 358 were first-time recipients: 187 received the SVV and 171 the WVV. The questionnaire was returned by 333 (93%) of the subjects; most returned it within 1 week and all within 5 weeks. These 333 workers were comparable with respect to age, sex, occupation and time of vaccination (Table 1).

None of the participants experienced an immediate allergic reaction after the vaccination. More

than 80% reported some form of adverse effect (Table 2); most were WVV recipients (86% v. 78%,  $p = 0.039$ ). Complaints related to the injection site predominated (Table 2); the most common was arm soreness (Table 3), reported by 119 SVV recipients (68%) and 124 WVV recipients (78%) ( $p = 0.032$ ). There was no significant difference in reported severity of local soreness between the two groups (Table 3). On average, soreness lasted 1 to 2 days in both groups; however, it resolved within 12 hours after vaccination in a greater proportion of the SVV recipients (22% v. 10%,  $p = 0.013$ ). Analgesic medications were taken by 14% of the SVV recipients and 19% of the WVV recipients (the difference was not significant [ $p = 0.13$ ]). Visible local reactions (redness or swelling or both) were reported more often by the WVV recipients than by the SVV recipients (Table 3,  $p = 0.013$ ).

Systemic reactions were reported by a similar proportion of respondents in each group (Table 3). Examining the primary outcome measure we found that there were fewer complaints of generalized aching in the SVV group than in the WVV group (23 [13%] of 174 v. 41 [26%] of 159,  $p = 0.0028$ ). Younger vaccinees (those 35 years or less) complained more often of generalized aching than the older ones did (16% v. 8% for the SVV recipients and 26% v. 21% for the WVV recipients); however, these differences were not statistically significant. Other complaints (Table 3) were of diverse nature and may not all have been due to vaccination. The

Table 1: Characteristics of hospital workers enrolled in voluntary influenza vaccination program in the 1989-90 season

Characteristic	Vaccine; no. (and %) of patients	
	Split-virion vaccine (SVV) (n = 174)	Whole-virion vaccine (WVV) (n = 159)
Age, yr		
Mean (and standard deviation)	35.1 (9.5)	36.5 (9.8)
Range	18-65	18-72
Sex		
Female	129 (74)	119 (75)
Male	45 (26)	40 (25)
Occupation		
Nurse	39 (22)	33 (21)
Physician	21 (12)	27 (17)
Laboratory technician	23 (13)	27 (17)
Administration	13 (7)	8 (5)
Other*	78 (45)	64 (40)
Time of vaccination		
End of shift	43 (25)	43 (27)
Before or during shift	107 (61)	96 (60)
On or before day off	20 (11)	18 (11)
Unknown	4 (2)	2 (1)

\*Includes physical, occupational and respiratory therapists, radiology technicians, students and porters.



rates of such complaints did not differ significantly between the two groups. Reports of probable intercurrent gastrointestinal or respiratory illness were equally frequent in the two groups (Table 3).

Four (2%) of the SVV recipients and three (2%) of the WVV recipients reported missing work because of symptoms they attributed to vaccination. However, in three cases the reason for absenteeism appeared to be an intercurrent illness (cough, severe

vomiting or migraine); this left two cases (1%) of vaccine-related absenteeism in each group.

The volunteers who had received influenza vaccine previously were the same as those in the controlled study in terms of age, sex, occupation and time of vaccination. The rates of local and systemic adverse reactions to WVV were virtually identical to the rate in the group of first-time WVV recipients. Generalized aching occurred in 31 (19%) of 162

Table 2: Outcome of influenza vaccination

Outcome	Vaccine; no. (and %) of patients		p value*
	SVV	WVV	
Any adverse effects	136 (78)	137 (86)	0.039
Any local adverse effects	122 (70)	129 (81)	0.013
Any systemic adverse effects	58 (33)	66 (42)	0.077
Local adverse effects only	78 (45)	71 (45)	NS
Local and systemic adverse effects	44 (25)	58 (36)	0.018
Systemic adverse effects only	14 (8)	8 (5)	NS
No adverse effects reported	33 (20)†	20 (13)†	0.066

\*NS = not significant.  
†Denominator excludes recipients who did not answer all questions (nine in SVV group and six in WVV group).

Table 3: Adverse effects reported by the vaccine recipients

Adverse effect	Vaccine; no. (and %) of patients		p value
	SVV	WVV	
<b>Local effects</b>			
Any	122 (70)	129 (81)	0.013
Any soreness	119 (68)	124 (78)	0.032
Soreness to touch*	41 (24)	34 (21)	
Soreness with arm movement*	61 (35)	69 (43)	
Constant aching*	14 (8)	18 (11)	
Soreness duration, h			0.03
1-12	24 (14)	11 (7)	
13-24	30 (17)	29 (18)	
25-48	47 (27)	61 (38)	
> 48	8 (5)	8 (5)	
Redness or swelling	29 (18)§	44 (29)§	0.013
<b>Systemic effects</b>			
Any	58 (33)	66 (42)	0.77
Generalized aching	23 (13)	41 (26)	0.0028
Tiredness	32 (18)	38 (24)	
Headache	19 (11)	26 (16)	
Chills	11 (6)	13 (8)	
Fever	16 (9)	13 (8)	
Gastrointestinal symptoms†	9 (5)	8 (5)	
Respiratory symptoms‡	6 (3)	3 (2)	
Other	3¶ (2)	2   (1)	

\*Maximum pain reported.  
†Includes one or more of the following: nausea, vomiting, abdominal cramps, appetite loss and diarrhea.  
‡Includes one or more of the following: runny nose, cough, sore throat and tight chest.  
§Denominator excludes recipients who did not answer all questions.  
¶Includes one each: stiff neck, dizziness, irritated eyes.  
||Includes one each: backache, painful axillary lymph nodes.

volunteers, a rate not significantly different from that among the WVV recipients in the controlled study.

Most of the vaccinees (in all three groups) rated the subsequent reactions as tolerable or minor. Over 96% indicated that they would accept vaccination the next season.

## Discussion

Of the adverse reactions commonly associated with influenza vaccination, generalized aching (malaise and myalgia) is the most debilitating. We believe that the difference in the reported rates of generalized aching between the two groups resulted from true differences in reactogenicity of the vaccines used. Potential sources of bias were extensively controlled. The products differed only in terms of the final ether treatment to split the influenza virions. By selection the subjects were healthy and inexperienced with influenza vaccine; inclusion of those with varying experience might have biased both the occurrence and the perception of adverse effects. The randomly determined groups were well matched, particularly in terms of age and sex, factors known to influence rates of adverse reactions to influenza vaccines.<sup>8,9</sup> The vaccines were given by two highly skilled nurses who had no further contact with the subjects. The symptom questionnaire form was in a check-box format and consisted mainly of closed questions; the return rate (93%) was excellent, and almost all of the forms were fully completed. The data entry was completed off site by a technician unaware of the premise of the study. The number of participants was large enough to reveal a 50% reduction in rates of generalized aching with a power of 90% ( $\alpha = 0.05$ , one-sided).

The actual rates of reported adverse reactions were higher than usually encountered except in studies involving health care workers<sup>7,8</sup> and young adults.<sup>10</sup> Health care workers are perhaps more attentive to minor reactions than other recipients and are more apt to report them when invited to do so. This could be particularly true for first-time vaccinees. Our subjects might have been particularly attuned to adverse effects because we advised them of the high rates encountered in our previous study.<sup>7</sup> Without a placebo control group we cannot distinguish between vaccine-induced symptoms and intercurrent illness, particularly of a mild nature. In one placebo-controlled study involving elderly patients<sup>11</sup> symptoms such as headache, tiredness and chills occurred with appreciable frequency in the placebo recipients. The rate of coincidental illness might be higher among employees of a children's hospital than among other health care workers, given the greater prominence of respiratory tract infections among

pediatric inpatients, although we have no comparative data. Our immunization program was completed well before the onset of influenza activity in our community in 1989.<sup>12</sup>

Although statistically significant, the difference between the two groups in the occurrence of local adverse reactions was small and of little practical significance. This negligible difference is consistent with other comparisons of WVV and SVV.<sup>8,13</sup> In a recent placebo-controlled study of SVV involving hospital workers Weingarten and associates<sup>14</sup> found that arm soreness was reported by 51% in the SVV group and by 7% in the placebo group ( $p < 0.01$ ) and that redness was reported by 11% and 0% respectively ( $p < 0.05$ ). The observed rates of reactions to SVV were similar to the rates in our study.

Our study subjects were encouraged to receive the vaccines at the end of their work shifts or before their days off when convenient. This conferred no apparent advantage in terms of reducing local soreness. Those vaccinated before or during work were no more likely than the others to complain of arm soreness with movement (40% v. 46%), constant aching at the injection site (11% v. 7%) or soreness that persisted more than 24 hours (39% v. 37%); none of these differences was statistically significant. This observation supports the use of "on-the-job" strategies, such as mobile immunization carts<sup>15</sup> and lunch-time drop-in clinics, to maximize vaccine coverage.

The most frequent systemic symptoms after influenza vaccination are generalized aching, muscle soreness and fever occurring within 12 hours and lasting 1 to 2 days.<sup>2,3,7,8,16,17</sup> Those who have limited experience with influenza virus antigens (e.g., children and young adults) are most often affected, particularly after their first exposure to the vaccine.<sup>18</sup> Mostow and collaborators<sup>8</sup> noted malaise and myalgia after vaccination with WVV in 37% of subjects under 25 years of age, as compared with 21% of those over 40 ( $p < 0.0001$ ). Similarly, Wise and colleagues<sup>10</sup> found that 34% of WVV recipients under 35 years reported systemic symptoms, as compared with 7% of those over 35 ( $p < 0.005$ ).

The use of SVV has been associated with fewer systemic adverse effects,<sup>8,13,18</sup> especially in children,<sup>2,3</sup> without a reduction in immunogenicity.<sup>2,3,13,18</sup> SVV is now routinely used in children. Young adults, such as those targeted in hospital programs, can also benefit from SVV.<sup>8,13</sup> In our study the use of SVV reduced the rate of generalized aching to half that among the WVV recipients ( $p < 0.0028$ ).

The rate of absenteeism attributed to vaccination did not differ between the two groups. In half the instances the cause appeared to be an intercurrent illness rather than the vaccine. A baseline rate of absenteeism for this population is not available.

Despite the high reported rate of minor adverse events 96% of the subjects agreed to receive influenza vaccine the following season. Since the participants represented only 25% of the staff members offered vaccine future acceptance rates will not necessarily improve even with use of SVV.

We conclude that the routine use of SVV preparations in young adults would reduce the risk of the most severe adverse reactions and likely increase acceptability of vaccination programs aimed at such people. Older vaccinees would likely also benefit. In Canada SVV is licensed for use in adults and has an immunogenicity equivalent to that of WVV;<sup>2,13,18</sup> however, the latter is supplied almost exclusively because of its lower cost. In the United States only SVV has been marketed for adults in recent years. With expanded use its cost was reduced to that of WVV. Consumers and immunization programs could be well served if manufacturers effected a similar change to SVV in Canada.

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## Not the whole story

*It is certainly a one-sided opinion — even though generally adopted at the moment — that all infectious agents which are still unknown must be bacteria. Why should not other microorganisms just as well be able to exist as parasites in the body of animals?*

— Robert Koch (1843-1910)