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# Inactivated Influenza Vaccination for People With Spinal Cord Injury

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## Abstract

**Objective—**To examine the antibody responses of people with spinal cord injury (SCI) to the commercially available trivalent influenza vaccine.

**Design—**Prospective trial of patients and controls.

**Setting—**Veterans Affairs medical center.

**Participants—**Forty people with SCI and 40 able-bodied subjects.

**Intervention—**Intramuscular administration of inactivated influenza vaccine.

**Main Outcome Measures—**Antibody responses were determined by using the standard hemagglutination-inhibition test before and 4 weeks after vaccination. Serum antibody responses were assessed as follows: (1) percentage of each cohort achieving a 4-fold or greater rise in antibody titer, (2) percentage of each cohort achieving a postvaccination antibody titer of 32 or more, and (3) postvaccination geometric mean antibody titers.

**Results—**The serum antibody responses to each vaccine antigen were similar for the SCI and the control cohorts for the 3 outcomes. Neither the time since injury (≤1y vs >1y) nor the level of injury (paraplegia vs quadriplegia) affected the vaccine antibody responses in the SCI cohort. Subjects older than 65 years had lower postvaccination serum antibody levels than those younger than 65 years ($P<.05$).

**Conclusions—**People with SCI responded to influenza vaccination in a manner similar to able-bodied subjects and would be expected to benefit from vaccination.

### Keywords

Antibody response; Immunity; Influenza vaccine; Rehabilitation; Spinal cord injuries

EACH YEAR, INFLUENZA infects an average of about 65 million Americans, of whom approximately 114,000 are hospitalized and 36,000 die.[1,2] Serious illness and death occur most frequently in people 65 years of age or older or in people of any age who have medical



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conditions that predispose them to complications of influenza. Vaccination is the primary method for preventing influenza3; it has proven benefit in reducing influenza-related work absenteeism, visits to physicians' offices, hospitalizations, and deaths.[4–7] Groups targeted for vaccination because of increased risk for complications from influenza include people 65 years of age or older, residents of chronic care facilities, adults with chronic pulmonary disorders, and adults who have required regular medical follow-up in the preceding year because of chronic medical disorders.[3] In people with spinal cord injury (SCI), the incidence of death from pneumonia and influenza is higher than in the general population; pneumonia is the leading cause of death among SCI survivors.[8,9] Thus, most people with SCI would be expected to benefit from annual influenza vaccination. However, adequacy of the antibody response of people with SCI to the inactivated influenza vaccine has not been documented.

Several researchers have postulated a role for the central nervous system in regulating the immune system.[10–12] SCI may disrupt this regulatory process and thus impair the immune response. In this context, we investigated the antibody response of SCI subjects versus that of able-bodied subjects to the commercially available, trivalent, inactivated influenza vaccine. We also evaluated the potential effect of age, time since injury, and level of injury on that antibody response.

## METHODS

### Participants

Forty people with SCI (mean age, 41y) from the SCI inpatient unit and outpatient clinic at the Veterans Affairs medical center in Houston, TX, were enrolled in the study. Forty able-bodied subjects (mean age, 54y) from the ambulatory care clinics, the inpatient medicine service, and the nursing home at the same medical center were enrolled as the control cohort. Inclusion criteria included age greater than 18 years and being at increased risk of complications from influenza. Exclusion criteria included an active influenza infection, a history of allergic reaction to influenza vaccine or its components, current receipt of influenza prophylaxis (amantadine), or inability to obtain informed consent. This study was approved by the appropriate institutional review boards.

### Vaccination

In mid-October 1994, all subjects received a 0.5-mL intramuscular injection of trivalent influenza vaccine from the same lot. The vaccine contained 15μg each of A/Texas/36/91 (H1N1), A/Shangdong/9/93 (H3N2), and B/Panama/4/90 hemagglutinin antigens.[a]

### Antibody Assay

Serum samples were obtained from each subject immediately before and 4 weeks after immunization and stored at −20°C until analysis. Paired sera from each subject were tested simultaneously by the standard hemagglutination inhibition assay using the virus strains in the vaccine as antigens.[13] Geometric mean antibody titers (GMTs) were calculated.

### Response Measures

Serum antibody responses to the 3 vaccine antigens were assessed as follows: (1) pre- and postvaccination $\log_2$ GMTs, (2) the percentage of each cohort that achieved a serologic response (a ≥4-fold rise in antibody titer), and (3) the percentage of each cohort that achieved an antibody titer of 1:32 or more (the antibody titer that is commonly accepted as protective).[14,15]

[a]**Suppliers** Parke-Davis, Division of Warner-Lambert Co, 201 Tabor Rd, Morris Plains, NJ 07950.

### Statistical Methods

Data analyses were performed by using the statistical software package SPSS, version 10.0.5,[b] for Windows. The *t* test for independent samples was used to compare means of the different groups (SCI, control, paraplegics, quadriplegics, people <65 or ≥65y of age) for continuous variables such as postvaccination GMT and age. Chi-square analyses were used to compare categoric variables such as whether a 4-fold rise in antibody titer occurred or whether a serum antibody titer (≥1:32) was achieved. Assuming a standard deviation (SD) of 1.5 $\log_2$, a sample size of 36 subjects in each cohort would yield an 80% power at an α of .05 to detect a 1 $\log_2$ difference (2-fold) in postvaccination antibody titers between cohorts.

## RESULTS

The control cohort (mean age, 41y) was significantly younger than the SCI group (mean age, 54y; 95% confidence interval difference, −6 to −20). Eleven of 40 (28%) SCI subjects were 65 years of age or older, whereas 7 of 40 (18%) control subjects were in that age group. More subjects in the control cohort (22/40) than the SCI cohort (15/40) had received the influenza vaccine in the year before the study, but this difference was not significant (*P*=.12). The serum antibody responses to each vaccine antigen were similar for the SCI and the control cohorts for all 3 outcomes (table 1). Specifically, the control group and the SCI group did not differ significantly in terms of the postvaccination GMTs (*P*>0.4 for all 3 antigens), the percentage of each cohort achieving a 4-fold rise in antibody titers (*P*>0.6 for all 3 antigens), or the percentage of each cohort that achieved postvaccination antibody titers of 1:32 or more (*P*>0.6 for all 3 antigens).

Among the SCI subjects, 25 had paraplegia and 15 had quadriplegia. The subjects with paraplegia (mean age, 53y; mean time since injury, 14mo) and with quadriplegia (mean age, 56y; mean time since injury, 11mo) did not differ significantly in age (*P*>0.5) or in time since injury (*P*>0.3). Analysis of the 40 subjects in the SCI cohort did not reveal any effect of level of injury (paraplegia vs quadriplegia) or time since injury (≤1y vs >1y) on the vaccine antibody responses.

As shown in other studies,[16] people more than 65 years of age had lower postvaccination serum antibody levels than younger subjects (*P*<.05 for comparing postvaccination GMTs by age to each of the 3 antigens) (table 1). Age over 65 years also was associated with a significant reduction in the percentage of subjects achieving a 4-fold or greater increase in serum antibody titer to each antigen (*P* values for the 3 antigens: H1N1, *P*=.006; H3N2, *P*=.13; B, *P*=.002).

## DISCUSSION

Although the SCI population is not listed by the US Center for Disease Control and Prevention as a group targeted for annual influenza vaccination,[3] several factors mandate annual vaccination of nearly all people with SCI. First, pneumonia and influenza are the leading causes of death in the first 12 years after SCI.[8,9] Mechanisms by which SCI may predispose to pneumonia include respiratory muscle dysfunction, impaired cough reflex, impaired ability to clear secretions, atelectasis, and malnutrition.[17–19] Second, as life expectancies improve for people with SCI,[8] this group has more opportunity to develop age-related chronic medical conditions. Indeed, in our study, 28% of the SCI subjects were 65 years of age or older. Also, people of all ages with SCI have a much higher incidence of chronic medical conditions, such as urinary system disorders and pressure ulcers, than the general population.[9] In the elderly population at large, influenza vaccination decreases the risk of hospitalization for pneumonia

[b]SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

or influenza and also reduces the risk of death from all causes.[4,7,20] Risk reduction also has been found for people with chronic lung disease, cardiovascular disease, immunosuppression, diabetes, renal disease, stroke, and other chronic medical conditions.[7,21] Thus, the confluence in the SCI population of the physiologic changes the injury imposes on the respiratory system, secondary medical complications of SCI, and chronic age-associated conditions suggests that nearly all people with SCI would benefit from annual influenza vaccination.

Nonetheless, the benefit of influenza vaccination for the SCI population is assumed rather than proven. The high incidence of infectious complications in the SCI population has led several researchers to postulate a link between SCI and depression of immune function. Skin integrity and a preserved cough reflex are basic immune defense mechanisms that are frequently impaired by SCI. However, on a cellular level, some studies have found impaired lymphocyte proliferative responses and impaired neutrophil phagocytic function in people with SCI.[11,12] The difference in neutrophil function was noted in patients with tetraplegia but not with paraplegia, suggesting that injury below the level of sympathetic outflow tracts does not affect this type of immune response. The theory of centralized neurologic control of the immune system is supported by the discovery that both primary and secondary lymphoid tissues are directly innervated by sympathetic nerve endings, and leucocytes have functional adrenergic receptors on their surfaces. However, the etiology of any immune impairment in people with SCI is probably multifactorial, with suboptimal nutrition and stress-induced immunosuppression having significant roles.[10]

In contrast to these reports of impaired cellular immunity, impairment of the humoral immune response has not been documented in the SCI population. Specifically, 2 studies in which pneumococcal polysaccharide vaccine was given to SCI subjects found that their antibody response did not differ from that of able-bodied controls.[19,22] One of these studies documented normal nutritional status of SCI subjects and also examined the impact of level of injury; it did not find an effect of the level of injury on the antibody response to pneumococcal vaccination.[22] Results of these studies are in accord with our findings in this study of the inactivated influenza vaccine, and they suggest that the humoral immune response is functionally preserved in people with SCI.

Our study had several limitations. It was not powered to detect less than a 2-fold difference in postvaccination antibody levels between the cohorts. Such a difference could be considered clinically relevant. Although our sample size was small, we did confirm that elderly people had a significantly less robust antibody response to influenza vaccination than younger people, thus showing that our sample population behaved as expected based on data from prior studies.[16] Our 2 cohorts were not matched in terms of age. However, the younger ages of the control cohort would tend to skew results toward a stronger antibody response in that cohort because younger people tend to have a more robust humoral response to inactivated influenza vaccine.[3] Additionally, a greater number of subjects in the control cohort had received influenza vaccination in the prior year than had subjects in the SCI cohort. Immune response is attenuated in patients with a history of influenza vaccination and in those who have high prevaccination titers.[23,24] In our study, neither the percentages in each cohort with prior vaccination nor the prevaccination titers differed significantly, so it is unlikely that prior vaccination status affected our results.

An adequate antibody response to influenza vaccination does not necessarily confer protection against influenza. However, given the concern that SCI itself can impair immune responses, our finding that the antibody responses of subjects with SCI to inactivated influenza vaccine is similar to that of able-bodied people is reassuring. Because the number of people with SCI living in the United States is approximately 230,000,[25] the population is not large enough to provide direct proof of the benefit of influenza vaccination. Also, a randomized, placebo-

controlled trial of influenza vaccination in the SCI population is not ethically acceptable. Our finding that people with SCI mount an appropriate antibody response to inactivated influenza vaccine suggests that annual influenza vaccination is a reasonable preventive strategy for the SCI population.

## CONCLUSIONS

Influenza and its complications are a major source of morbidity and mortality in the SCI population. The primary preventive measure for influenza is an annual influenza vaccination. In this study, we found that a cohort with SCI had a response similar to that of an able-bodied cohort to inactivated influenza vaccination. Thus, people with SCI would be expected to benefit from annual influenza vaccination.

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## References

1. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–86. [PubMed: 12517228]
2. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. J Infect Dis 2000;181:831–7. [PubMed: 10720501]
3. Bridges CB, Harper SA, Fukuda K, et al. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP) [published erratum in: MMWR Morb Mortal Wkly Rep 2003;52:526]. MMWR Recomm Rep 2003;52(RR-8):1–34. quiz CE1–4.
4. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med 2003;348:1322–32. [PubMed: 12672859]
5. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 1994;331:778–84. [PubMed: 8065407]
6. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med 1995;333:889–93. [PubMed: 7666874]
7. Hak E, Nordin J, Wei F, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. Clin Infect Dis 2002;35:370–7. [PubMed: 12145718]
8. Soden RJ, Walsh J, Middleton JW, Craven ML, Rutkowski SB, Yeo JD. Causes of death after spinal cord injury. Spinal Cord 2000;38:604–10. [PubMed: 11093321]
9. DeVivo MJ, Black KJ, Stover SL. Causes of death during the first 12 years after spinal cord injury. Arch Phys Med Rehabil 1993;74:248–54. [PubMed: 8439250]
10. Cruse JM, Keith JC, Bryant ML, Lewis RE. Immune system-neuroendocrine dysregulation in spinal cord injury. Immunol Res 1996;15:306–14. [PubMed: 8988397]
11. Campagnolo DI, Keller SE, DeLisa JA, Glick TJ, Sipski ML, Schleifer SJ. Alteration of immune system function in tetraplegics. Am J Phys Med Rehabil 1994;73:387–93. [PubMed: 7993612]
12. Campagnolo DI, Bartlett JA, Keller SE, Sanchez W, Oza RF. Impaired phagocytosis of *Staphylococcus aureus* in complete tetraplegics. Am J Phys Med Rehabil 1997;76:276–80. [PubMed: 9267186]
13. Miller GL, Stanley WM. Quantitative aspects of the red blood cell agglutination test for influenza virus. J Exp Med 1944;79:185–95. [PubMed: 19871362]
14. Potter CW. Determinants of immunity to influenza infection in man. Br Med Bull 1979;35:69–75. [PubMed: 367490]

15. Beyer WE, de Bruijn IA, Palache AM, Westendorp RG, Osterhaus DM. Protection against influenza after annually repeated vaccination. Arch Intern Med 1999;159:182–8. [PubMed: 9927102]

16. Couch RB. Prevention and treatment of influenza. N Engl J Med 2000;343:1778–87. [PubMed: 11114318]

17. Reines HD, Harris RC. Pulmonary complications of acute spinal cord injuries. Neurosurgery 1987;21:193–6. [PubMed: 3658131]

18. Fishburn MJ, Marino RJ, Ditunno JF. Atelectasis and pneumonia in acute spinal cord injury. Arch Phys Med Rehabil 1990;71:197–200. [PubMed: 2317137]

19. Darouiche RO, Groover J, Rowland J, Musher DM. Pneumococcal vaccination for patients with spinal cord injury. Arch Phys Med Rehabil 1993;74:1354–7. [PubMed: 8259905]

20. Nichol KL, Wuorenma J, Von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998;158:1769–76. [PubMed: 9738606]

21. Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. Ann Intern Med 1999;130:397–403. [PubMed: 10068413]

22. Lynch AC, Palmer C, Lynch AC, et al. Nutritional and immune status following spinal cord injury: a case controlled study. Spinal Cord 2002;40:627–30. [PubMed: 12483495]

23. Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. Vaccine 2002;20:1099–105. [PubMed: 11803070]

24. Atmar RL, Keitel WA, Cate TR, Quarles JM, Couch RB. Comparison of trivalent cold-adapted recombinant (CR) influenza virus vaccine with monovalent CR vaccines in healthy unselected adults. J Infect Dis 1995;172:253–7. [PubMed: 7797925]

25. Darouiche, RO. Infections in patients with spinal cord injury. In: Mandell, G.; Bennett, J.; Dolin, R., editors. Principles and practice of infectious disease. Churchill Livingstone; Philadelphia: 2000. p. 3159-63.

**Table 1**

Antibody Responses to Influenza Vaccine Antigens

| Vaccine Antigens | SCI (n=40) | No SCI (n=40) | Age <65y (n=62) | Age ≥65y (n=18) | Paraplegia (n=25) | Quadriplegia (n=15) |
|---|---|---|---|---|---|---|
| A/Texas/36/91 (H1N1) | | | | | | |
| Prevaccination GMTs ± SD ($log_2$) | 3.78 ± 1.94 | 3.72 ± 1.75 | 3.97 ± 1.96 | 3.00 ± 1.08* | 3.56 ± 1.87 | 4.13 ± 2.07 |
| Postvaccination GMTs ± SD ($log_2$) | 5.68 ± 1.95 | 5.50 ± 1.69 | 5.92 ± 1.75 | 4.44 ± 1.62* | 5.56 ± 2.04 | 5.86 ± 1.84 |
| % with ≥4-fold antibody rise | 50 | 58 | 58 | 39 | 52 | 47 |
| % with postvaccination antibody ≥32 | 70 | 75 | 81 | 44* | 72 | 67 |
| A/Shangdong/9/93 (H3N2) | | | | | | |
| Prevaccination GMTs ± SD ($log_2$) | 3.20 ± 1.50 | 3.68 ± 1.70 | 3.47 ± 1.60 | 3.33 ± 1.72 | 3.20 ± 1.55 | 3.20 ± 1.47 |
| Postvaccination GMTs ± SD ($log_2$) | 5.05 ± 1.62 | 5.30 ± 1.36 | 5.35 ± 1.45 | 4.56 ± 1.50* | 5.12 ± 1.72 | 4.93 ± 1.49 |
| % with ≥4-fold antibody rise | 60 | 68 | 69 | 44 | 64 | 53 |
| % with postvaccination antibody ≥32 | 68 | 68 | 73 | 50 | 72 | 60 |
| B/Panama/4/90 | | | | | | |
| Prevaccination GMTs ± SD ($log_2$) | 2.90 ± 0.96 | 3.20 ± 1.48 | 3.16 ± 1.28 | 2.67 ± 1.08 | 2.76 ± 0.78 | 3.13 ± 1.19 |
| Postvaccination GMTs ± SD ($log_2$) | 4.65 ± 1.27 | 4.67 ± 1.12 | 4.84 ± 1.18 | 4.06 ± 1.06* | 4.64 ± 1.35 | 4.67 ± 1.17 |
| % with ≥4-fold antibody rise | 60 | 58 | 65 | 39 | 68 | 47 |
| % with postvaccination antibody ≥32 | 60 | 53 | 66 | 22* | 60 | 60 |

*$P$<.05 vs <65 group.

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