Original Research

Efficacy of the Influenza Vaccine in Patients with Malignant Lymphoma

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**Background:** The benefits and efficacy of the influenza vaccine have been controversial and have had mixed reviews in the recent literature. Immunosuppressed patients and those receiving chemotherapy are particularly at risk for infectious complications and are therefore given high priority to receiving prophylactic vaccines.

**Method:** We administered the influenza vaccine to 29 patients with malignant lymphoma who were receiving chemotherapy or had recently completed therapy during the flu season of 2003-2004. An aged-matched control group received the same vaccine during the same period. The ability of both groups to mount a protective titer of antibodies to the antigens in the vaccine was measured.

**Results:** Three of 29 patients (10%) in the lymphoma group were able to mount a 4-fold titer to at least one of the influenza A antigens. One patient developed a protective titer to both influenza A and B antigens and 3 of 29 responded to the influenza B antigen. In the control group 13 of 29 (45%) responded to an influenza A antigen and 14 of 29 (48%) had a 4-fold response to the B antigen. Seven of 29 controls (24%) had a 4-fold increase in their titers to both the A and B antigens.

**Conclusions:** This study confirmed the low incidence of response or efficacy to the influenza vaccine reported in previous studies. Only a small percentage (10%) of immunosuppressed patients with malignant lymphoma responded with a 4-fold increase in their antibody titer to the major antigens of the 2003 influenza vaccine. Most interestingly, less than 50% of the aged-matched control population studied responded with a 4-fold increase in their antibody titer. Additional studies are needed to determine methods for improving the efficacy of the vaccine and the effectiveness of the influenza vaccination program in preventing influenza infections in the United States.

**Keywords:** Antigens, Influenza, Lymphoma, Titer, Vaccine

Influenza is an important cause of morbidity and mortality worldwide. The elderly and those with underlying medical illnesses appear to be particularly vulnerable populations for influenza infection. Vaccination for individuals who are at increased risk for influenza infection and influenza-associated pneumonia has been recommended by the Centers for Disease Control and Prevention. This would include the elderly, individuals who have chronic disease or a malignancy, and those who are currently receiving immunosuppressive medications (e.g., corticosteroids, chemotherapy). The efficacy of this immunization program is often difficult to quantify since most studies in the current literature use surrogate endpoints and the parameters used to determine the response to vaccines vary from study to study. Pre- and post-immunization serum antibody titers are commonly used to measure the immunological response, with a 4-fold increase in antibody titer accepted as being indicative of vaccine efficacy. However, given the list of recommended immunizations for adults, it is unlikely that titers to determine the efficacy of each vaccine are measured and recorded subsequent to administration. Nowhere is this issue more
compromised by advanced age and aggressive chemotherapy and the patient’s immune system is often further lymphoreticular malignancies are inherently immunosuppressive immunologic response to a variety of vaccines. In particular, individuals with malignant diseases to mount an adequate vaccine efficacy and effectiveness. Numerous studies have individuals with vaccines further compounds the problem of and cell culture techniques to isolate and identify the virus. antibody testing, polymerase chain reaction (PCR) analysis and pneumonia (flu-like illness), that are interpreted as general malaise, headache, musculoskeletal aches and pains and nonspecific systemic and subjective symptoms, e.g., fever, infection. Most large studies on this subject use a variety of nonspecific systemic and subjective symptoms, e.g., fever, general malaise, headache, musculoskeletal aches and pains and pneumonia (flu-like illness), that are interpreted as representing the flu or influenza infection. These symptoms are frequently experienced in association with a host of other viral infections. Few of these studies document actual influenza viral infection by using direct fluorescence antibody testing, polymerase chain reaction (PCR) analysis and cell culture techniques to isolate and identify the virus.

The issue of providing protection to immunocompromised individuals with vaccines further compounds the problem of vaccine efficacy and effectiveness. Numerous studies have shown the inability of the immunocompromised host and individuals with malignant diseases to mount an adequate immunologic response to a variety of vaccines. In particular, lymphoreticular malignancies are inherently immunosuppressive and the patient’s immune system is often further compromised by advanced age and aggressive chemotherapy regimens.

In this study we enrolled 29 patients with a diagnosis of malignant lymphoma (Hodgkin’s disease and non-Hodgkin’s lymphoma) who were being treated with standard chemotherapy regimens or who had completed their chemotherapy within 3 months prior to receiving the influenza vaccine. Influenza antibody titers to the three antigens that constitute the vaccine were measured in each subject prior to administration of the vaccine and at various intervals thereafter to determine efficacy. The results were compared to those for age and gender-matched controls.

Materials and Methods
Study design
Twenty-nine patients with a diagnosis of malignant lymphoma (27 non-Hodgkin’s lymphoma and 2 Hodgkin’s disease) and 29 age- and gender-matched controls were acquired from the Marshfield Clinic healthcare system in Wisconsin. Subjects were required to be at least 18 years of age and have a life expectancy of at least 6 months. Age range for the lymphoma group (cases) was 32-81 years of age (median age 62 years). Age range in the control group was 35-82 years of age (median age 61 years). Subjects were excluded from eligibility into the study if they had a history of the following: (1) known or suspected allergy to eggs or egg products, (2) received immunoglobulins within the previous 90 days prior to vaccination or would be receiving immunoglobulins during the 60 days post-vaccination, (3) had a bone marrow or solid organ transplant, (4) planning to receive another vaccine during the study period, (5) were receiving corticosteroids (7.5 mg of prednisone minimum dose or its equivalent), (6) had an acute febrile illness at the time of vaccination, (7) Guillain-Barré syndrome, (8) neutropenia as defined by a white blood cell count of <1.0 x 10^9/l or lymphopenia defined as a lymphocyte count of 1.0 x 10^9/l. Twenty-one of the lymphoma patients in the case group were in the process of receiving chemotherapy; 8 had completed their chemotherapy within 3 months of entrance into the study. A mean of 27 days occurred from the last chemotherapy cycle start date to the administration of the influenza vaccine. The majority of cases had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 signifying their ability to carry out normal daily activities with minimal signs and symptoms related to their disease.

Titers to the 3 major antigens contained in the vaccine were measured prior to its administration and again at 4, 12 and 24 weeks subsequent to vaccination for all study participants (cases and controls). A trivalent purified antigen vaccine, FLUVIRIN (Chiron Corp., Liverpool, England), containing antigens of type A (New Caledonia/20/99 [H1N1] and Panama/2007/99 [H3N2]) and type B (HongKong/330/2001-like virus) influenza virus, was administered intramuscularly into the deltoid area of the upper arm using a 1 inch #25 gauge disposable needle during the 2003 influenza season (October through December). Each 0.5 µl of vaccine contained 15 µg of each influenza A and B hemagglutinin. Antibody titers to each of the 3 antigens were measured pre- and post-administration of the vaccine by means of the hemagglutinin inhibition test.

Collection of patient sera
Approximately 10 ml of blood was drawn from study participants. Each sample was refrigerated for 30 minutes and then centrifuged at 1800 x g at 4°C for 15 minutes. Serum was collected from each tube, transferred into appropriately labeled 1.8 ml Cryule vials (Wheaton, Millville, NJ) and stored at -80°C until assayed.

Influenza antigens and sera
Antigens and control sera were provided by Dr. Henrietta Hall, Centers for Disease Control and Prevention (CDC). Two influenza A antigens (New Caledonia/20/99 [H1N1] and Panama/2007/99 [H3N2]) and two influenza B antigens (B/Brisbane/32/02 and B/Sichuan/379/99) were used to determine patients’ serum titers in a hemagglutination inhibition assay. Because antigen to the B/Hong Kong/330/01-like virus hemagglutinin was not available
through CDC, antigens of two very closely related viruses (B/Brisbane/32/02 and B/Sichuan/379/99) were used instead. In addition, control sera specific for each of the respective antigens were used to validate the assay. The lyophilized influenza A and B antigens were reconstituted in sterile distilled water and subjected to a hemagglutination assay to determine the number of hemagglutinating units (HAU) present or the amount of virus needed to agglutinate an equal volume of a standardized red blood cell (RBC) suspension.

Receptor-destroying enzyme treatment of sera
Sera were treated with receptor-destroying enzyme (RDE; Sigma-Aldrich, St. Louis, MO) as described elsewhere.24 The lyophilized product was reconstituted with 5 ml sterile distilled water, diluted with 100 ml calcium saline (pH 7.2), aliquoted and stored at –20°C. RDE was combined with each sera sample in a 4:1 ratio (0.4 ml RDE: 0.1 ml serum) and incubated overnight at 37°C. Following the overnight incubation, 5 volumes (0.5 ml) of 1.5% sodium citrate were added to each sample and incubated for 30 minutes at 56°C to inactivate the remaining RDE.

Standardization of RBCs
Five milliliters of chicken RBCs (Rockland Immunochemicals, Inc., Gilbertsville, PA) were centrifuged at 1200 rpm for 10 minutes and the supernatant aspirated. The remaining RBCs were gently resuspended in 50 ml sterile distilled water, diluted with 100 ml calcium saline (pH 7.2) and centrifuged at 1200 rpm for 5 minutes. The supernatant was aspirated and the RBCs washed 2 additional times before being resuspended to a final volume of 20 ml in a 50 ml conical centrifuge tube. The concentration adjusted to reach a 5% suspension.

Hemagglutination assay
Each influenza antigen was serially 2-fold diluted in PBS (pH 7.2) across a V-shaped well microtiter plate to yield a volume of 50 µl. PBS alone was added to several wells to use as an assay control. After adding standardized RBCs (50 µl) to each well, the plate was agitated and incubated at room temperature for 30 minutes. Hemagglutination titers were read as the reciprocal of the serum dilution necessary to remove agglutination-inhibiting antibodies.

Hemagglutination inhibition assay
Sera samples from each of the collected timepoints were assayed for reactivity to both influenza A and B antigens using a previously described World Health Organization protocol.24 Briefly, RDE-treated sera were serially 2-fold diluted in PBS (pH 7.2) to reach a volume of 25 µl. An equal volume (25 µl) of appropriately diluted antigen (as determined by the hemagglutination assay; standard final HAU for the hemagglutination inhibition assay is 4 HAU) was added to each well receiving test sera. Additionally, wells were reserved for RBC control as well as back-titration for assay validation. The plates were agitated and incubated at room temperature for 15 minutes before 50 µl of standardized RBCs were added to each well on the plate. The plate was agitated again to mix well and incubated at room temperature for 30 minutes. Hemagglutination inhibition titers were read as the reciprocal of the serum dilution necessary to remove agglutination-inhibiting antibodies.

Statistical analysis
Titers converted to logarithmic scale, geometric means and 95% confidence intervals were used for comparisons between the cases and the controls. Data were recorded as geometric mean titers of antibodies, mean increase in antibody titer, protection rate and response rate to hemagglutinin proteins. Comparisons in mean titer levels were made between cases and controls, separately at baseline, 1, 3 and 6 months. The statistical p-value was derived based on a Wilcoxon signed rank test for paired data. All statistical tests were two-sided and a p-value of <0.05 was considered to be statistically significant. The effect of previous vaccination status on vaccine efficacy and effectiveness was compared to those vaccinated in the past 5 years. Vaccine effectiveness was descriptive since the incidence of actual influenza cases observed was small. A proportional comparison between cases and controls using McNemar’s test was done to determine whether the status of the titer was associated with lack of protection (titer ≥40 after vaccination, but with a pre-vaccination titer <40) as well as response rate (i.e., 4-fold increase in titer after vaccination).

Results
Three (10%) of the 29 subjects in lymphoma group (cases) and 13 (45%) in the control group had a mean increase in titers to one of the major antigens of influenza A (signed-rank test with a p-value of <0.05) at baseline and at 3 and 6 months for H3N2. Nine patients (31%) in the case group and 14 (48%) in the control group had a 4-fold increase in titer to one of the major antigens (Sichuan and Hong Kong) of influenza B (signed-rank test p <0.05 at baseline) at 1 and 3 months. Six (20%) of the controls responded to both influenza B antigens.

In the lymphoma group, those that developed an adequate antibody titer (4-fold increase) did so at 12 weeks with the exception of 1 patient who developed a 4-fold increase at 4 weeks, while those in the control group had a 4-fold increase in their titer at 4 weeks subsequent to the administration of the vaccine which persisted at the 12 week interval.

A statistically significant 4-fold rise in antibody titer was found between the two groups for H1N1 at baseline and at 1 and 3 months for H3N2 antigen. There was no statistically significant difference in 4-fold rise in the antibody titer to influenza B antigens between the two groups (table 1). None of the patients in the lymphoma group responded to both A and B antigens, while 7 (24%) controls had a 4-fold titer to both A and B antigens contained in the vaccine.

There was no statistically significant difference in the frequency of previous influenza vaccines administered in the past 5 years between the two groups (72% cases vs. 48%

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>GMT</th>
<th>p-value</th>
<th>Protection*</th>
<th>p-value</th>
<th>4-fold change/ response</th>
<th>p-value</th>
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<td>8%</td>
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<td>7%</td>
<td>0.4142</td>
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<tr>
<td><strong>B/Sichuan/379/99</strong></td>
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<td>251.97</td>
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</tbody>
</table>

*Titer ≥40 after vaccination but with pre-vaccination titer <40.

GMT, geometric mean titer. NA, not applicable.
weaker immune response than younger individuals.\textsuperscript{35-37} Been demonstrated that older age individuals tend to have a
malignancies.\textsuperscript{29-33} Prior exposure to influenza virus and
vaccines, including influenza vaccines, as compared to
responses to multi-antigen vaccines as well as single antigen
disease and non-Hodgkin’ s lymphoma have demonstrated poor

titers measured subsequent to the

Discussion
Most immunocompetent persons develop an effective
immune response to influenza A and B within 10 to 14 days
after vaccination.\textsuperscript{25-27} However, the inability to mount an
adequate or protective titer of antibodies to a variety of
vaccines in large segments of the population is well
documented and the efficacy of certain vaccines has been
difficult to determine.

High-risk segments of the population are identified as
dividuals who suffer from chronic illnesses, are on
corticosteroids or other immunosuppressive agents, have a
diagnosis of a malignant disease, are receiving chemotherapy
and the elderly population of our society at large. Ironically,
these are the very same groups that have the lowest response
to vaccines by virtue of a compromise in their immune status.

Patients with a diagnosis of cancer and who are actively
undergoing treatment are particularly at risk for acute and
chronic infections and are, therefore, given priority in most
vaccination programs being advocated. The literature,
however, suggests that many of these individuals will have an
inadequate response or be unable to develop a protective
antibody titer to a variety of vaccines being administered.\textsuperscript{28}

Serologic conversion rates of 19\%-93\% have been reported in
adults with various malignancies, but patients with Hodgkin’s
disease and non-Hodgkin’s lymphoma have demonstrated poor
responses to multi-antigen vaccines as well as single antigen
vaccines, including influenza vaccines, as compared to
patients with solid tumors or non-hematologic
malignancies.\textsuperscript{29-33} Prior exposure to influenza virus and
previous influenza vaccinations have also been shown to
suppress the production of antibodies and therefore influence
the response to new influenza vaccines.\textsuperscript{34} Additionally, it has
been demonstrated that older age individuals tend to have a
weaker immune response than younger individuals.\textsuperscript{35-37}

This study selected a homogenous group of patients with a
hematologic malignancy (lymphoma) and confirmed the low
incidence of response or efficacies of the influenza vaccine
administered during the fall of 2003 (October 1 through
December 20). Our sample size of lymphoma patients is too
small to comment on the degree of immunosuppression
caused by the various chemotherapeutic regimens used to
treat this group of patients, however, given the low percentage
of response it would appear that the immunosuppression, as
is determined by the antibody titers measured subsequent to the

vaccination, was not related to a specific regimen or agent
used in treatment.

It also demonstrated a surprisingly low response (41\%) of the
age-matched control group who had no history of medical
illness or medications that would render them
immunocompromised during the study period. Thus, it
appears that more effective vaccination programs may be
necessary to protect those individuals deemed at risk from
contracting communicable infections. Multiple studies have
shown that a second dose of influenza vaccine can enhance
the antibody response in both children and adults receiving
chemotherapy who mounted an inadequate immunologic
response to the initial dose.\textsuperscript{38-41} Whether the administration
of additional or “booster” doses, or increasing the
concentration of the antigen contained within the vaccine\textsuperscript{42,43}
will improve the effectiveness of the vaccine remains to be
determined.

Our study, although small, raises two important questions: (1)
how effective is the influenza vaccine in preventing an acute
influenza viral infection in individuals at increased risk of
infection, i.e., the immunocompromised host? And (2), how
effective is the influenza vaccine in preventing influenza viral
infection in the general population who receives the vaccine
each year?

Given the nonspecific and surrogate endpoints used to
acquire these data without clear documentation of an
influenza infection in the currently available literature, the
incidence of influenza infection may be significantly
overestimated. To support this contention, a recent update
study on influenza activity in the United States showed that of
the 130,577 respiratory specimens for influenza viruses
acquired from collaborating laboratories throughout the
country from individuals with “flu-like illnesses,” only
24,649 (18.9\%) were positive.\textsuperscript{44} Thus, the influenza
vaccination program may be more effective in preventing
infection than previously estimated in a recently published
study assessing the effectiveness of the influenza vaccine
among children and adults.\textsuperscript{44}

The strengths of our study include: (1) all cases tested for
response had lymphoma and were exposed in a recent
timeframe to immunosuppressive therapy, and (2) patient
population (cases) and age-matched controls were all
vaccinated and subsequently evaluated at the same institution.
However, our study is limited by the small number of patients
enrolled from which conclusions could be drawn and by the
assumption that a 4-fold rise in antibody titer subsequent to the
vaccination is representative of a positive response or a
protective titer.

Large multicenter studies will be necessary to obtain accurate
data to answer these important questions. Only then will we
be able to determine the cost-benefit of the current influenza
vaccination program.
Acknowledgments

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References


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28. Robertson JD, Nagesh K, Jowitt SN, Dougal M, Anderson H, Stargardt in the preparation of this manuscript.


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