conclusion that any delay in vaccination can only increase the risk of herpes zoster.

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In reply—Risk of Disseminated Varicella Zoster in Immunosuppressed Patients Receiving Zoster Vaccination

We thank Dr Bubb for his interest in our study and appreciate the opportunity to respond to his questions and concerns. Specifically, concern was raised about our conclusion that our findings "support the current recommendations for zoster vaccination in that patients should withhold their immunosuppressants for 4 weeks before immunization,"[1] even though we found no cases of disseminated varicella zoster among 4826 vaccinated individuals who were taking immunosuppressant medication. Additional concerns centered on our findings related to herpes zoster, specifically that (1) our data revealing a higher risk of herpes zoster in immunosuppressed patients who stopped immunosuppressive therapy argue that it would be prudent to vaccinate immunosuppressed patients as soon as possible, (2) the data do not support withholding immunosuppressant therapy for a minimum of 4 weeks before vaccination compared with any other arbitrarily chosen interval, and (3) vaccination is unlikely to be the cause of the increased risk of zoster during the 42 days postvaccination in the current vs remote immunosuppressant users.

Dr Bubb brings up good points, and we should have been clearer in our concluding remarks about withholding immunosuppressants. Current guidelines state that high-dose corticosteroids should be withheld for 4 weeks before administering the zoster vaccine, but the vaccine can be given to individuals taking low-dose corticosteroids without stopping therapy.[2,3] The results from our investigation suggest that there is a low risk of disseminated herpes zoster associated with the zoster vaccine when given to patients currently using immunosuppressant medications. However, it should be kept in mind that most of the patients in this study were receiving low-dose corticosteroids; too few patients were taking high-dose corticosteroids (n=550) at the time of vaccination to determine any associations or draw any inferences. Therefore, our results regarding disseminated varicella zoster support the recommendation to vaccinate patients taking low-dose corticosteroids without stopping therapy, but there is insufficient evidence to recommend vaccinating patients taking high-dose corticosteroids without stopping treatment. We recognize that our concluding statement could have been better stated.

According to Dr Bubb, the data confirm that "immunosuppression increases the risk of herpes zoster even after stopping immunosuppressive therapy" and suggest that "it would be prudent to vaccinate immunosuppressed patients as soon as possible to minimize the time-dependent risk of herpes zoster." The rate of herpes zoster for the remote immunosuppressant user group in our study was 15 cases per 1000 person-years, which is indeed higher than the rate of herpes zoster in nonimmunocompromised individuals (range, 6.0-8.6 cases per 1000 person-years among adults 60-79 years of age)[4] but is in fact consistent with rates of herpes zoster reported in patients with immune-mediated diseases, which range from as low as 6.4 to as high as 32.5 cases per 1000 patient-years.[5-9]

Regarding the choice of the 4-week interval for withholding therapy, the evidence supporting the recommendation to withhold immunosuppressants for 4 weeks before administering a live virus vaccine has never been strong. These recommendations, however, are not arbitrary but reflect the opinion of experts and are in part based on knowledge of the time it takes for the hypothalamic-pituitary-adrenal axis to recover from prolonged immunosuppression with corticosteroids. In our study, patients were classified as remote users if the immunosuppressant was stopped a minimum of 4 weeks before vaccination and as current users if the immunosuppressant was continued into this time frame. With lower rates of herpes zoster in the remote user group, our study results provide some evidence to support the recommendation to withhold immunosuppressants for 4 weeks before vaccination. Because most of the patients in this study were taking low-dose corticosteroids, the question then becomes whether low-dose corticosteroids should be stopped before vaccination. We do not believe that the results from this study, by themselves, support stopping low-dose corticosteroids before vaccination.

Our finding that the risk of herpes zoster was increased in the 42 days following vaccination in the current vs remote exposure group is complex because several factors are potentially at work. The study was designed to include a cohort of patients who, at baseline, have a higher risk of herpes zoster; the only observable difference between the comparison groups was current vs remote use of immunosuppressants. As

stated in the "Discussion" section of our article, it is unlikely that the herpes zoster experienced by these patients was caused by the vaccine virus strain. In this regard, we agree with Dr Bubb that vaccination is unlikely to be the cause of the increased risk of zoster during the 42 days postvaccination in the current immunosuppressant users. However, there are several potential explanations for our findings: (1) administration of the vaccine could possibly trigger herpes zoster in response to the antigen load in some immunosuppressed patients, (2) current immunosuppressant use could delay the immune response to the zoster vaccine, leading to a higher risk of herpes zoster in a population already at risk (ie, as an indicator of immune response, peak antibody levels after zoster vaccination in elderly individuals without immune-mediated diseases is 21 days[10] but is likely longer in patients receiving immunosuppressants), (3) current immunosuppressant use by itself could increase the risk of herpes zoster, and (4) current use of immunosuppressants could indicate a population that is fundamentally different from remote users in ways that are not captured using an observational design.

In conclusion, we agree that patients with certain immune-mediated diseases are at a higher risk of herpes zoster, and therefore, measures should be undertaken to maximize immunization of these individuals with the zoster vaccine in a safe and effective manner.

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New Oral Anticoagulants in Elderly Adults With Chronic Kidney Disease

To the Editor: I read with interest the review article by Ponticelli et al[1] on drug management in the elderly adult with chronic kidney disease (CKD) that was published in the May 2015 issue of *Mayo Clinic Proceedings* and agree with their recommendations. Of note, the section on oral anticoagulants does not include or comment on the 4 new oral anticoagulants (NOAs) that have been approved by the US Food and Drug Administration (FDA) over the past 5 years. The NOAs approved are dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and, recently, edoxaban (Savaysa).[2,3]

Atrial fibrillation (AF) is a common disorder in elderly adults. About 12% of AF cases occur in adults 75 to 84 years of age, and more than 33% of patients with AF are 80 years or older. Atrial fibrillation has a global prevalence of about 33.5 million cases and an incidence of approximately 5 million new cases per year. Atrial fibrillation is associated with a 5-fold increased risk of stroke. In the United States, AF accounts for more than 467,000 hospital admissions and more than 99,000 deaths per year.[4] Recently, the NOAs have been gradually replacing warfarin, a vitamin K antagonist that was the standard of care for about 60 years. Thus, I offer a few additional comments for the primary care physician, including the need for renal risk stratification when using the NOAs.[2,3]

Typically, the vitamin K antagonist drugs are used for AF in patients with prosthetic heart valves, mitral valve stenosis, severe valvular disease, or severe renal dysfunction, whereas the NOAs are mostly indicated for nonvalvular AF. The field of NOA is evolving, and new indications, boxed warnings, and precautions have been added since their initial approval by the FDA.[3,5-8]

The first NOA approved in the United States was dabigatran, and its approval was based mostly on the RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial that randomized participants to either warfarin or 1 of 2 doses of dabigatran (110 mg or 150 mg twice daily).[9] The FDA did not approve the 110-mg dose. The FDA approved the dose of 150 mg twice daily in all patients, including patients with a creatinine