

Clues on Limiting Herpes Virus Reactivation

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Herpes zoster (shingles) is caused by reactivation of varicella zoster virus. Live attenuated zoster strain vOka vaccine is currently approved to prevent varicella zoster reactivation in persons over 50 years of age. The vaccine reduces the risk of shingles by 70% in persons aged 50–59 and 51%–55% in persons ≥ 60 years, so is only partially effective in the elderly, the most susceptible group. The mechanisms by which the vaccine reduces shingles risk are largely unknown, although it is clear that both arms of adaptive immunity (B-cells and T-cells) are boosted. A more extensive characterization of the immune response generated by the boost and a classification of the peptides that induce an immune response are needed to design a more effective preventive strategy. "We believe more efficacious vaccines could be developed if the mechanisms of protection were better understood", explains Dr. Kerry Laing, first author of a paper published in the April issue of *Journal of Infectious Diseases*.

In a collaborative research effort among researchers from Fred Hutch, University of Washington and the Center for Disease Control and Prevention, the immune responses of 12 subjects receiving the zoster boost were characterized. An initial increase in CD4 T-cell response that peaked at day 14 and decayed at month 6, mainly targeted two proteins of the virus, the opening reading frames (ORF) 40 and 67, followed by other 9 different ORFs. Interestingly, boosting not only increased the magnitude but also the breadth of the response: the boost in T-cell magnitude mirrored an increase in the number of unique viral proteins against which T-cells reacted. Therefore, the increased breadth of the response following vaccination might be part of its mechanism of action and thus important for blocking viral reactivation.

While this study focused on CD4 T-cell responses, future work will also focus on the effect of the boost on CD8 T-cells: "Of course, we are poised to extend our investigation CD8+ T-cell immunity with our complete antigen set to see what clues that cell-type will show us," said Dr Laing.

The study analyzes the response to zoster vaccination and opens the way to the design of more effective vaccines. However, the reported results also raise questions about what immune response is needed for protection. In fact, increasing the level or breadth of T-cells alone may not be enough to protect from viral reactivation: protection may need, instead, a response to the "right" set of peptides. "Using our complete set of viral proteins to compare responses in people protected by

zoster vaccination versus people not protected would be a great benefit to understanding this further," proposed Dr. Laing.

This knowledge could conceivably facilitate the development of similar vaccines for related alphaherpesviruses (HSV1 and HSV2), for which there is no current cure or effective vaccine. In fact, as the zoster vaccine is the only FDA-approved therapeutic vaccine currently on the market, it offers a wealth of opportunity to understand how the immune system may work to control recurrent infections.

[Laing KJ, Russell RM, Dong L, Schmid DS, Stern M, Magaret A, Haas JG, Johnston C, Wald A, Koelle DM. 2015. Zoster vaccination increases the breadth of CD4+ T cells responsive to varicella zoster virus. Journal of Infectious Diseases. Epub ahead of print.](#)

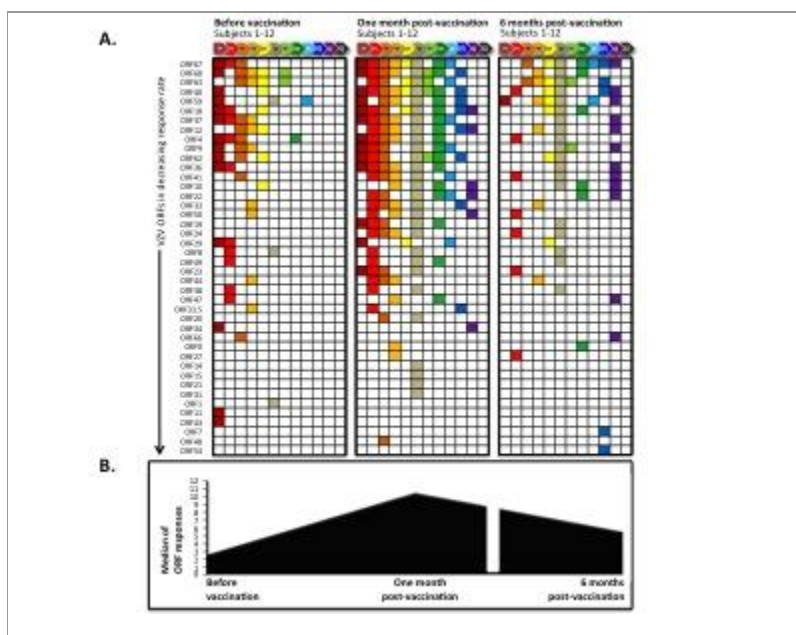


Image provided by Dr. Kerry Laing

T-cell responses before and after zoster vaccination in 12 study subjects (A). The median number of ORF responses in the cohort increased approximately 4-fold following vaccination ($P = .0495$), returning to approximately 2-fold above baseline after 6 months ($P > .999$) (B).