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Effect of Varicella-Zoster Virus (VZV) Fluorescent-Antibody-to-Membrane-Antigen (FAMA) Testing on Sensitivity of Determining VZV Immunity in Healthcare Workers and on Furlough Days

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Immunity to varicella-zoster virus (VZV) is particularly important for healthcare workers (HCWs). Susceptible HCWs are not only at risk of developing disease but also at risk of transmitting the infection to vulnerable hospital patients. Complicating this issue is that the incubation period for varicella is both lengthy and variable. The incubation period ranges from 10 to 21 days, with a mean of 15 days. More importantly, individuals who have been infected may be contagious for up to 48 hours before the development of the rash, thus making transmission of disease fairly unpredictable.^{1,2} VZV is one of the most highly infectious viruses, requiring the furlough of exposed susceptible HCWs during the entire incubation period (days 10–21 after exposure). This can stress the exposed individual and can economically impact the hospital. In one 1988 study, the cost of 54 furloughed employees was almost \$40,000 per year.³

Documentation of varicella immunity in HCWs is important, regardless of whether HCWs have had natural infection or have been vaccinated. Studies have shown that, before vaccination, from 1.6% to 16% of HCWs are susceptible to the VZV by serologic testing.⁴ Personal recall of disease is not an accurate measure of immune status.^{4,5} Accurate assays of VZV immunity are therefore of obvious importance.

We sought to evaluate the postvaccination VZV fluorescent-antibody-to-membrane-antigen (FAMA)–documented immune status of HCWs who, when tested by the commonly employed and commercially available VZV enzyme-linked immunosorbent assay (ELISA), were found to be not immune to varicella. Our objective was to compare the results of VZV FAMA tests with those obtained by use of a commercially available VZV ELISA in a

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population of HCWs who were believed to be susceptible to varicella. If the FAMA test proved to be more accurate for this purpose than the ELISA, fewer furloughs of HCWs exposed to varicella should result.

A retrospective review of VZV ELISA results was performed on employees at Memorial Sloan Kettering Cancer Center (MSKCC; New York, New York). Employees who were documented by results of previous VZV ELISA serology (VIDAS Varicella-Zoster IgG Enzyme-Linked Fluorescent Assay; bioMérieux) to be susceptible to varicella from 2002 through 2007 were identified through review of the database at MSKCC's Employee Health and Wellness Services. Only those individuals who were persistently susceptible to VZV (defined by a VZV ELISA result of "susceptible" or "equivocal") after having received at least 2 doses of the varicella vaccine were included in the study. Those individuals without documentation of vaccination were excluded from the study, because hospital protocol is to first administer 2 doses of the vaccine to employees determined by VZV ELISA to be susceptible to varicella. Those identified employees who did not seroconvert by VZV ELISA after varicella vaccination were considered to be persistently susceptible to chickenpox and subsequently were included in the study.

The serum samples that had previously been tested using the VZV ELISA method were still accessible, because they had been stored at -20°C . in the MSKCC Clinical Microbiology Laboratory. They were subsequently sent to Columbia University (New York, New York) to be tested using the VZV FAMA method.⁶

The VZV FAMA method is considered to be the standard method against which other methods for determining varicella immunity are measured.⁷⁻⁹ A VZV FAMA titer of at least 1:4 indicates immunity to varicella. All VZV FAMA testing was performed during 2007 and 2008. In 2007, it became standard procedure at MSKCC to test all VZV ELISA nonimmune results by the VZV FAMA method.

A chart review was performed to determine demographic characteristics and to identify "susceptible" employees who were furloughed secondary to exposure to VZV. Furlough days taken by individuals who received at least 2 doses of varicella vaccine, who were found to be susceptible by VZV ELISA, and who were subsequently found to be immune by VZV FAMA testing, were considered to be "avoidable" furlough days.

A total of 67 employees were evaluated for varicella immunity by VZV FAMA testing. The mean age of the employees was 36.0 years (range, 20–64 years). Forty-eight employees (72%) were female (mean age, 34.7 years [range, 20–64 years]). Nineteen employees (28%) were male (mean age, 39.2 years [range, 24–63 years]).

Forty-seven (70%) of 67 employees tested using the VZV FAMA method were found to be immune to VZV despite being deemed susceptible by previous VZV ELISA. A total of 91 furlough days had been taken by these 47 employees. Fifty-nine of these furlough days were determined to have been avoidable on the basis of VZV FAMA results. The remaining furlough days were not identified as avoidable for the purposes of the study, because those furlough days occurred before vaccination. As noted above, because vaccination was a

prerequisite for inclusion in this study, only furlough days taken after vaccination but before confirmation of immunity by VZV FAMA testing were accepted as avoidable.

Although several assays for the determination of VZV immunity have been developed, the most commonly used test is the ELISA, because it is automated and relatively easy to perform. However, sensitivity has been documented to be variable and sometimes poor, with study-dependent sensitivities for natural immunity ranging from 43% to 92%, compared with FAMA.¹⁰ Postvaccination viral antibody titers tend to be lower than those seen in natural immunity, and ELISA sensitivities likewise tend to be lower.¹⁰ Thus, the potential to underestimate immunity in populations such as HCWs exists. As a result, other potential tests of varicella immunity have been sought.

FAMA testing was developed more than 30 years ago and is widely considered to be the most reliable test for determination of the immune status of a patient with regard to varicella.^{7–10} FAMA test sensitivity has been documented to be more than 95%. The FAMA test is more sensitive after vaccination than the ELISA, which is only 63%–76% as sensitive in comparison.¹⁰

The VZV FAMA test does have substantial limitations. It is technically difficult, requiring the use of live cells rather than extracts. Because of its technical requirements, automation has not been possible. Also, interpretation of the test relies on the subjectivity of the technician, who needs to be extremely skilled and experienced to ensure the most accurate results. These limitations have, in turn, interfered with the general availability of this methodology.^{8,10}

Our study, however, suggests that the current VZV ELISA is not sensitive enough to provide an accurate indication of varicella immunity in HCWs. A more accurate test in this population would be beneficial in many ways. As these results illustrate, the increased sensitivity of FAMA testing would prevent the unnecessary vaccination of individuals who are already immune and, consequently, would prevent the risks associated with vaccination. Likewise, it would prevent the costs associated with administration of 2 vaccines as well as with laboratory confirmation of vaccine-induced immunity.

Also, unnecessary furlough days can be avoided and can even be eliminated. The exposure of a susceptible HCW to VZV necessitates furlough from work for as much as 12 days. This is a substantial period of time with excess cost to the institution, which must find alternate staffing to cover the furloughed employee's shifts. A more accurate test would benefit both the institution, by eliminating unnecessary expense, and the employee, by sparing the anxiety and frustration of furlough.

An important goal is to find a test for VZV immunity that is more sensitive than the VZV ELISA. This test must be easily performed and must be widely available to minimize the shortcomings of the current testing process. Additional investigation is needed.

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