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Comparative Performance of Herpes Simplex Virus Type 1-Specific Serologic Assays from MRL and Meridian Diagnostics

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Two companies, MRL and Meridian Diagnostics, have developed Food and Drug Administration-approved herpes simplex virus type 1 type-specific enzyme immunoassays. The sensitivity, specificity, and overall testing efficiency of these assays were 98.2, 93.8, and 96.6% for MRL and 98.8, 99.0, and 98.1% for Meridian, making both of these kits suitable for use in the clinical lab.

The herpes simplex viruses (herpes simplex virus type 1 [HSV-1] and HSV-2) are important causes of disease worldwide. HSV-1 is the primary cause of oral-facial and pharyngeal herpes infections and may cause herpetic whitlow, eye infections, and disseminated disease (1, 2, 8, 15). HSV-1 also accounts for 10 to 15% of all genital herpetic infections (3, 6, 11). The proportion of genital infections with HSV-1 is reportedly even higher in some locations (4, 10, 13).

Transmission of HSV-1 occurs following contact with fluid from vesicular lesions or contact with infected body fluids, such as saliva and genital secretions (4, 8, 9). Although HSV-1 has historically been acquired primarily in childhood, acquisition of the virus is now often seen during early adulthood (4, 8, 9). Seroprevalence studies from several sites worldwide have indicated that approximately 60 to 70% of adolescents have not developed antibodies to this virus and are therefore still susceptible to infection with HSV-1 (5, 7, 8).

HSV-1 serostatus is also important with regard to the vaccine developed for HSV-2. The usefulness of the vaccine appears to be linked to the HSV-1 serostatus of the individual being immunized. Only female recipients with a negative HSV-1 serostatus prior to immunization appear to derive benefit from this vaccine (S. Spruance and The Herpes Vaccine Efficacy Study Group, Abstr. Addendum 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. L-6, p. 22, 2000). This, coupled with the role of HSV-1 as a significant etiologic agent for herpes genitalis, produces the need for a reliable HSV-1 immunoglobulin G (IgG) type-specific assay. This report focuses on the head-to-head comparison of two Food and Drug Administration (FDA)-approved HSV-1 type-specific EIAs.

Serum from 532 blood donor specimens was collected from the Central Kentucky Blood Center, Lexington, Ky., and frozen in 2-ml aliquots at −70°C until testing. Serologic evaluation of HSV-1 antibodies was performed using glycoprotein G type-specific enzyme immunoassays from Meridian Diagnostics Inc. (Cincinnati, Ohio) and from MRL Diagnostics (Cypress, Calif.). All testing was performed according to the manufacturers' specifications. Absorbances were read on an automated ELx800 Universal Microplate Reader (Bio-Tek Instruments Inc.) at 405 nm for the Meridian assays and 450 nm for the MRL assays. For both manufacturers, absorbency cutoff values were those established by validation studies with a mean absorbency value: those with >0.99 times the reference absorbency were interpreted as positive, those with 0.91 to 0.99 times the reference absorption were interpreted as equivocal, and those with less than 0.91 times the reference were interpreted as negative. All samples with concordant results were interpreted as true positives or true negatives for both assays. Additionally, 13.7% of all HSV-1-concurrent results and all discordant results were confirmed by immunoblotting, which is considered the "gold standard" for antibody identification. For this study, the MRL Immunoblot IgG Assay (MRL Diagnostics) was used according to the manufacturer's guidelines.

The 532 specimens collected from healthy blood donors were tested in parallel using both the MRL and the Meridian enzyme immunoassay (EIA) kits. Of these specimens, 327 produced concordant HSV-1-positive test results and 179 produced concordant HSV-1-negative test results. The remaining 26 specimens produced discordant test results.

Twenty-eight results from the 26 discordant specimens were

TABLE 1. HSV-1 EIA discrepant results

Result no.	MRL result	Meridian result	Resolved result	Discrepancy classification	No. seen	Comment
1	−	+	+	MRL false negative	4	
2	+	−	+	Meridian false negative	4	EIA values just below EQ
3	+	EQ[a]	+	Meridian equivocal	1	Strong band on blot
4	−	EQ	+	MRL false negative and Meridian equivocal	2	Blot bands just positive
5	+	−	−	MRL false positive	8	Low positive EIA
6	+	−	−	MRL false positive	4	No common antigen
7	−	+	−	Meridian false positive	2	Low positive EIA
8	−	EQ	−	Meridian equivocal	1	

[a] EQ, equivocal.

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TABLE 2. Performance characteristics of the Meridian and MRL HSV-1 type-specific EIAs

Parameter	Meridian result (%)	MRL result (%)
Sensitivity	98.8	98.2
Specificity	99.0	93.8
Negative predicative value	97.9	96.8
Positive predicative value	99.4	96.5
Efficiency[a]	98.1	96.6

[a] The value reflects all specimens tested, including those with equivocal results.

resolved, and the 73 HSV-1 concordant results (25 HSV-1 negatives and 48 HSV-1 positives) were confirmed using the HSV-1 and HSV-2 Immunoblot IgG. Immunoblot testing confirmed 100% of the concordant EIA results. The Meridian kit was found to have produced two false positives, four false negatives, and four equivocals. The MRL EIA produced 12 false-positive results and 6 false negatives (Table 1). Sensitivity, specificity, negative and positive predictive values, and overall testing efficiency for each assay were calculated using Baye's theorem (14) (Table 2).

Of the two EIA kits, Meridian's assay had slightly better overall performance characteristics than the MRL assay. The MRL assay's specificity was compromised due to the number of false-positive test results. When these false positives were analyzed, two main types of staining patterns were noted. First, a small number of samples (<1%) had HSV-1 bands but no demonstrable HSV common antigen band. These false positives were attributed to an antibody cross-reactivity to glycoprotein G1 that lacked any HSV common antigen specificity. A similar type of cross-reactivity has been noted in our laboratory for the MRL HSV-2 type-specific EIA (12). The majority of specimens seen as false positives with the MRL assay produced EIA values just above the equivocal range. These data suggest that a more conservative cutoff for the positive range might be indicated for the MRL assay.

Both assays demonstrated excellent sensitivity (98.8% for Meridian and 98.2% for MRL). The positive and negative predictive values and testing efficiency of these two assays likewise are excellent. Overall, either assay is adequate for patient testing in the laboratory setting.

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REFERENCES

1. **Arvin, A. M., and G.G. Pober.** 1999. Herpes simplex virus, p. 878–887. *In* P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, and R. H. Yolken (ed.), Manual of clinical microbiology, 7th ed. ASM Press, Washington, D.C.
2. **Bader, C., C. S. Crumpacker, L. E. Schnipper, B. Ransil, J. E. Clark, K. Arndt, and I. M. Freedberg.** 1978. The natural history of recurrent facial-oral infection with herpes simplex virus. J. Infect. Dis. **138:**897–905.
3. **Benedetti, J., L. Corey, and R. Ashley.** 1994. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann. Intern. Med. **121:**847–854.
4. **Brugha, R., K. Keersmaekers, A. Renton, and A. Meheus.** 1997. Genital herpes infection: a review. Int. J. Epidemiol. **26:**698–709.
5. **Christenson, B., M. Bottiger, A. Svensson, and S. Jeansson.** 1992. A 15-year surveillance study of antibodies to herpes simplex virus types 1 and 2 in a cohort of young girls. J. Infect. **25:**147–154.
6. **Corey, L., H. G. Adams, Z. A. Brown, and K. K. Holmes.** 1983. Genital herpes simplex infections: clinical manifestations, course, and complications. Ann. Intern. Med. **98:**958–972.
7. **Gibson, J. J., C. A. Hornung, G. R. Alexander, F. K. Lee, W.A. Potts, and A. J. Nahmias.** 1990. A cross-sectional study of herpes simplex virus types 1 and 2 in college students: occurrence and determinants of infection. J. Infect. Dis. **162:**306–312.
8. **Glezen, W., G. W. Fernald, and J. A. Lohr.** 1975. Acute respiratory disease of university students with special reference to the etiologic role of Herpesvirus hominis. Am. J. Epidemiol. **101:**111–121.
9. **Guinan, M. E., J. MacCalman, E. R. Kern, J. C. Overall, and S. L. Spruance.** 1981. The course of untreated recurrent genital herpes simplex infection in 27 women. N. Engl. J. Med. **304:**759–763.
10. **Kawana, T., T. Kawaguchi, and S. Sakamoto.** 1976. Clinical and virological studies on genital herpes. Lancet **ii:**964.
11. **Lowhagen, G., E. Jansen, E. Nordenfelt, and E. Lycke.** 1990. Epidemiology of genital herpes infections in Sweden. Acta Derm. Venereol. (Stockholm) **70:**330–334.
12. **Ribes, J. A., M. Hayes, A. Smith, J. L. Winters, and D. J. Baker.** 2001. Comparative performance of herpes simplex 2 virus type specific serologic assays from Meridian and MRL Diagnostics. J. Clin. Microbiol. **39:**3740–3742.
13. **Ribes, J. A., A. Steele, J. P. Seabolt, and D. J. Baker.** 2001. A six year study of the incidence of herpes in genital and nongenital cultures in a Central Kentucky Medical Center patient population. J. Clin. Microbiol. **39:**3321–3325.
14. **Winkel, P., and B. E. Statland.** 1991. Interpreting laboratory results: reference values and decision making, p. 49–76. *In* J. B. Henry (ed.), Clinical diagnosis and management by laboratory methods, 18th ed. W. B. Saunders Co., Philadelphia, Pa.
15. **Young, S. K., N. H. Rowe, and R. A. Buchanan.** 1976. A clinical study for the control of facial mucocutaneous herpes virus infections. I. Characterization of natural history in a professional school population. Oral Med. Oral Pathol. **41:**498–507.