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Letters to the Editor

Performance of Meridian ImmunoCard *Mycoplasma* Test in a Multicenter Clinical Trial

Alexander et al. describe the performance of the Meridian ImmunoCard *Mycoplasma* Test in a multicenter trial (1). The described test is a card-based enzyme-linked immunosorbent assay (ELISA), designed to detect immunoglobulin M (IgM) antibodies to *Mycoplasma pneumoniae*. Compared with consensus results, the ImmunoCard assay showed a sensitivity of 90% and a specificity of 93%. We have comments on the way the evaluation of the ImmunoCard *Mycoplasma* Test for serological diagnosis of *M. pneumoniae* infection was performed and on the conclusion that the ImmunoCard is appropriate for use to rapidly diagnose infection in patients with atypical pneumonia.

In their evaluation of the ImmunoCard assay, Alexander et al. defined consensus results as true positives (i.e., two or more of the following assays or analyses giving positive results: IgM-specific immunofluorescence assay [IFA], IgM-specific ELISA, the complement fixation test [CFT], and chart review) and true negatives (all other result combinations). The definition of consensus results as used by those authors has the following pitfalls. Firstly, diagnosis of an infection with *M. pneumoniae* based on two IgM-specific tests will miss cases in which no IgM response appears. As already indicated by Alexander et al. and as has been described in the literature, IgM response may be absent, e.g., in case of a reinfection (5, 6). On the other hand, just testing for IgM antibodies without evidence of IgG response can result in overdiagnosis of *M. pneumoniae* infections: the presence of shared antigens, or polyclonal stimulation of B lymphocytes by the infecting agent, can give rise to nonspecific or heterotypic increases in levels of IgM antibodies. Secondly, using the CFT for diagnosis of *M. pneumoniae* infection requires testing of paired serum samples (4). Otherwise, when testing a single serum sample, the first day of illness should be known in order to know if one is testing an acute-phase or a convalescent-phase serum sample. Without these data, reliable interpretation of CFT results remains difficult. Finally, the value of reviewing medical records to resolve equivocal laboratory results is questionable. Discrimination between *M. pneumoniae* and other (most viral) pathogens causing respiratory tract infections is difficult when based on clinical parameters only, as has been reported by Foy et al. (3). We had similar findings in a prospective study of children with respiratory tract infections: coryza was the only clinical parameter that was significantly correlated, albeit inversely, with an *M. pneumoniae* infection (2).

Even though the evaluation of the ImmunoCard assay is hampered by the limitations mentioned above, the test may be useful in rapid testing of patients with atypical pneumonia. However, if one relies on serology for diagnosis of an infection with *M. pneumoniae*, the test should always be used in combination with other, non-IgM-specific assays.

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Author's Reply

We thank Drs. Dorigo-Zetsma, Wertheim-van Dillen, and Spanjaard for their interest in our paper and their comments. While we agree in principle that consensus results are not without faults, we disagree with some of their specific points.

In their first comment, Dorigo-Zetsma et al. state that diagnosing an infection by using two IgM-specific tests may miss cases in which no IgM response occurs. This is true; however, we did not base our definition on two IgM-specific tests. We used two of four determinations, only two of which (the IFA and ELISA) were IgM specific, as an indication of a true positive. Complement fixation and chart review are not IgM specific, and thus we could pick up cases in which no IgM response was generated.

We have difficulty understanding the second comment of Dorigo-Zetsma et al., that IgG testing may be used to determine if a positive IgM response may be due to cross-reactivity or polyclonal stimulation of B cells. Although certain infectious agents, such as Epstein-Barr virus, can cause polyclonal B-cell activation and antibody production, we are unaware of documented clinical cases in the literature where detectable antibodies specific for *M. pneumoniae* antigens are produced as a result of polyclonal B-cell stimulation. Even if those antibodies do occur under certain conditions, testing a patient for *M. pneumoniae*-specific IgG will not differentiate a true IgM response from a heterophile antibody. A patient could have *M. pneumoniae*-specific IgG from a past infection and a current infection with the polyclonal stimulator. Although a convalescent-phase specimen may help to resolve this situation, we find that second specimens are rare in clinical laboratories and, in the era of managed care, will be even rarer.

We think that chart review, although subjective, is an important adjunct to clinical laboratory data and is often necessary for proper interpretation of a laboratory result. In our paper, we did not accept chart review alone as an indication of a true positive, but needed to combine the clinical presentation with at least one laboratory parameter, either an IgM-specific response or a complement fixation titer (64 in our study) shown to be consistent with a current or recent infection. In

our opinion, correlating laboratory and clinical data is an important part of the laboratorian's function.

As a final point, the purpose of our paper was not to show that IgM testing should be the sole method used to diagnose an *M. pneumoniae* infection. In contrast, we pointed out how the lack of a "gold standard" hampers any evaluation of *M. pneumoniae* serology, and in this point we are in complete agreement with Dorigo-Zetsma et al. We did show that the ImmunoCard kit performs favorably in comparison with other currently available methods.

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