Comparison of Four Commercially Available Avidity Tests for *Toxoplasma gondii*-Specific IgG Antibodies

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*Toxoplasma* infection in pregnant women may cause congenital toxoplasmosis. Diagnosis of infection is based on serological tests aimed at detecting IgM and IgG antibodies against *Toxoplasma gondii*. However, IgM antibodies are not an accurate marker for discriminating between acute and latent infection. Detection of residual or persistent IgM may occur months or even years after primary infection, while the IgG avidity test is a rapid means of identifying latent infections in pregnant women who exhibit both IgG and IgM anti-*Toxoplasma* antibodies on initial testing during pregnancy. In this study, we assessed and compared the performances of four commercially available *Toxoplasma* IgG avidity tests in immunocompetent and immunocompromised patients with acute and latent toxoplasmosis. The positive predictive value of high avidity to confirm latent toxoplasmosis was 100% for all the assays, indicating that high avidity is a hallmark of latent infection. However, the negative predictive value of high avidity ranged from 99.2% (bioMérieux) to 95.3% (Abbott), indicating that acute toxoplasmosis could not be reliably diagnosed based on low IgG avidity alone. Thus, the avidity test provides a rapid means for identifying latent *Toxoplasma* infection in immunocompetent pregnant women presenting both IgG and IgM anti-*Toxoplasma* antibodies on initial testing. In terms of cost-effectiveness, avidity testing is a powerful tool that optimizes screening and follow-up of pregnant women while minimizing the costs of screening by avoiding subsequent costly maternal and fetal investigation and unnecessary treatment. The cheapest assay, Vidas Toxo IgG Avidity, also had the best performance for the diagnosis of latent toxoplasmosis.

Toxoplasmosis is a widespread parasitic disease that usually causes no symptoms. However, infection in pregnant women may result in congenital toxoplasmosis (1). In France, a national program for detection and treatment of toxoplasmosis has reduced the rate and severity of congenital infections (2, 3). Diagnosis of toxoplasmosis is based on serological tests aimed at detecting IgM and IgG antibodies against *Toxoplasma gondii* (1, 4). However, these assays have been proven to be poorly reliable for discriminating between recent and latent infections. Indeed, detection of specific IgM antibodies, considered to be acute-phase markers, can lead to false-positive results or the detection of residual or persistent IgM months or even years after primary infection, suggesting that IgM is not an accurate acute-phase marker. In the obstetrical setting, determination of the date of infection is crucial to judge the necessity for antenatal diagnosis of toxoplasmosis (5).

For many years, IgG avidity assays have been used in the serological-screening strategy for pregnant women (6, 7). As these assays have been shown to be an essential tool for discriminating between acute and latent stages of infectious diseases, they are widely used in expert laboratories. Because in-house tests often lack automation and standardization, the use of commercial IgG avidity tests is highly recommended. For this purpose, most major *in vitro* diagnostic companies have produced kits based on various approaches, including recombinant antigen-based technology (8–12). Since 2006, the objective of the French National Reference Center for Toxoplasmosis (NRCT) has been to investigate the methods used for the serological diagnosis of toxoplasmosis, with the aim of reducing the cost of the French screening program (13). In this study, we assessed the performances of four commercially available *Toxoplasma* IgG avidity tests in defined populations of immunocompetent and immunocompromised patients with acute and latent toxoplasmosis.

**MATERIALS AND METHODS**

**Serum specimens.** A total of 206 sera were classified into three groups according to clinical and serological criteria, as follows (14).

(i) **Group 1**, acute toxoplasmosis. Sixty-seven samples from 56 pregnant women (one or two sera) corresponded to acute toxoplasmosis in pregnant women with confirmed seroconversion (appearance of IgG and IgM anti-*Toxoplasma* specific antibodies after an initial negative sample) and are therefore precisely dated. No immunocompromised patients were included in this group. The first sera were from untreated pregnant women, with all subsequent sera taken from patients treated with spiramycin or pyrimethamine-sulfadiazine.

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(ii) Group 2, latent toxoplasmosis with low IgG and negative IgM. Group 2 comprises 50 sera from 50 subjects with IgG at <50 IU/ml and negative for IgM, with a follow-up sample indicating no increase in IgG or presence of IgM. Nine of the patients were immunocompromised. In addition, there were 34 sera from subjects with a positive IgG history for >1 year and no IgM detected, including 11 immunocompromised patients.

(iii) Group 3, latent toxoplasmosis with positive IgG history for >1 year and positive IgM. Group 3 comprises 55 subjects, including 2 immunocompromised patients and 9 pregnant women more than 6 months pregnant, being treated during pregnancy after toxoplasma seroconversion.

All samples were selected using routine tests, including dye tests in reference laboratories from the NRCT network.

SEROLOGICAL DIAGNOSIS. (i) AVIORITY DETERMINATION. Four kits that are commercially available in France were tested, according to the manufacturers' recommendations.

(a) ARCHITECT TOXO IGG AVIORITY (ABBOTT). The Architect Toxo IgG avidity assay, European Community approved, is an automated test using a chemiluminescent microparticle immunosassay (CMIA) comprising two single tests that are both two-step immunosassays. One of the aliquots is treated with a blocking agent. The avidity of anti-Toxoplasma IgG in the sample is calculated using the relative light units (RLUs) of both tests. The percent avidity is obtained from the ratio of RLUs from the sample pre-treated with a blocking agent and those obtained from the unblocked sample. The avidity can be determined for samples tested with Architect Toxo IgG as ≥1.6 IU/ml. The avidities of specimens are classified as low (<50%), gray zone (50 to 59.9%), or high (≥60%). According to the manufacturer, an avidity of ≥60% allows the exclusion of an infection of less than 4 months.

(b) VIDAS TOXO IGG AVIORITY (BIO-MÉRIEUX). The Vidas Toxo IgG avidity, CE approved, is a semiautomated test combining a two-step enzyme immunoassay sandwich method with a final fluorescence detection (enzyme-linked fluorescence assay). It uses a dissociation agent, such as urea. The avidity can be determined only if the Vidas Toxo IgG II IgG is ≥8 IU/ml. Moreover, the Toxo IgG II IgG must be reduced to 15 IU/ml by sample dilution. For IgG titers between 8 and 15 IU/ml, samples can be used undiluted.

The avidity is determined by the ratio of the sample treated with the dissociated antigen to the nontreated sample. This allows the avidity of specimens to be classified as low (<0.2), gray zone (0.2 to 0.3), or high (≥0.3). According to the manufacturer, low avidity is not a proof of recent infection, whereas high avidity strongly suggests an infection of more than 4 months.

(c) PLATELIA TOXO IGG AVIORITY (DIASORIN). The Liaison Toxo IgG avidity II, CE approved, is an automated indirect immunoluminometric (competitive luminex immunoassay) test using urea as the dissociation agent. Responses are measured as RLUs, while the avidity is determined by the ratio of RLUs of urea-treated to those of nontreated samples. Avidity can be determined only if the Liaison IgG II IgG is ≥8.8 IU/ml and must be interpreted with caution if the IgG is <15 IU/ml. Avidity is classified as low (<0.3), gray zone (0.3 to 0.4), or high (≥0.4). According to the manufacturer, low avidity suggests a primary infection acquired within the last 4 months, although latent infection cannot be excluded. In contrast, high avidity excludes primary infection within the last 4 months.

(d) PLATELIA TOXO IGG AVIORITY (BIO-RAD). The Platelia Toxo IgG avidity, CE approved, is an indirect enzyme immunoassay in solid phase, which may be automated on a fully automated microplate processor (EVOLIS). It has to be used in association with the Platelia Toxo IgG test. IgG must be ≥9 IU/ml in order to determine the avidity. The test is based on a standard measurement of IgG followed by the same test after the addition of urea. The avidity is obtained from the ratio of the optical densities (OD) in the samples with and without urea. It allows the avidity to be classified as low (<0.4), gray zone (0.4 to 0.5), or high (≥0.5). According to the manufacturer, low avidity suggests recent infection of less than 20 weeks, although the result does not confirm this diagnosis with certitude, whereas high avidity suggests a past infection of over 20 weeks but does not exclude with certitude a more recent infection.

(ii) RETROSPECTIVE STUDY ON THE USE OF AVIORITY ASSAYS IN 16 FRENCH UNIVERSITY AND GENERAL HOSPITALS. We performed a retrospective study for 1 year to evaluate the use of avidity assays in patients presenting with positive Toxoplasma IgG and IgM results among 16 laboratories in our network. We have evaluated the number of avidity assays performed and their results.

STATISTICAL ANALYSIS. For the acute toxoplasmosis population, in an off-label use of the reagents, we estimated (i) the proportion of low-avidity results (sensitivity); (ii) the positive predictive value (PPV) and the negative predictive value (NPV) of a low-avidity result; (iii) the Youden index, measuring the accuracy of the test in detecting acute toxoplasmosis (negative index, ineffective test; index close to 1, effective test); and (iv) Yule's Q coefficient, measuring the correlation of the IgG avidity index with acute toxoplasmosis (the closer the coefficient to 1, the stronger the correlation). For the latent-toxoplasmosis population, in an approved use, similar biostatistical results were calculated using the proportion of high-avidity results. For all patients, equivocal or intermediate values were considered false negatives in subjects with acute toxoplasmosis and false positives in subjects with latent toxoplasmosis.

RESULTS

Comparison of the sensitivities of the four IgG avidity immunoassays for acute toxoplasmosis. The IgG kinetics, performed in parallel for the determination of the IgG avidity of each kit, followed similar courses with all kits (Fig. 1A). It should be borne in mind that the kinetics of IgG avidity varied considerably between patients. The Abbott test showed an increase in IgG avidity of 82.8% (23.8 at 2 to 4 weeks to 43.5% at 17 to 36 weeks postinfection). The bioMérieux test showed an increase of 56.3% (0.064 to 0.1), the Bio-Rad test 42.1% (0.19 to 0.27), and the DiaSorin test 30.1% (0.165 to 0.216). None of the sera exhibited high avidity even at 36 weeks postinfection (a late stage of infection). However, we have to bear in mind that all the sera taken from 6 to 8 weeks to 17 to 36 weeks postinfection were from pregnant women treated for acute toxoplasmosis (Fig. 1B).

The slow growth avidity maturation shortly postinfection was evident when the avidities were depicted for individual patients (Fig. 2). However, the existence of equivocal data showed differences between the four immunoassays (Table 1 and Fig. 2): 6 equivocal results for Abbott, 1 for bioMérieux, 2 for Bio-Rad, and 3 for DiaSorin. If these equivocal data were considered false negatives for detecting acute toxoplasmosis, then bioMérieux had the most appropriate capacity to recognize acute toxoplasmosis, with 98.2% sensitivity, followed by bio-Rad (96.4%), DiaSorin (94.6%), and finally Abbott (89.3%). Notably, no high-avidity results were found in this group, confirming the good sensitivity of these assays for the diagnosis of acute toxoplasmosis. It must be remembered that none of the kits is recommended for use in diagnosing acute toxoplasmosis.

Comparison of sensitivities for latent toxoplasmosis. Considering all patients with latent toxoplasmosis, the proportions of high-avidity results were 87.7% with bioMérieux, 87.1% with Abbott and DiaSorin, and 74.8% with Bio-Rad (Table 2 and Fig. 3 and 4). However, better results were obtained in the group of patients without specific IgM in the serum (group 2), with the proportion of high-avidity results reaching 94% for bioMérieux, 91.7% for Abbott and DiaSorin, and 83.3% for Bio-Rad. If the equivocal results were interpreted as low-avid-
ity results, the sensitivity was greatly diminished for each test, especially in the case of Bio-Rad, where a high number of equivocal results were observed. These false-negative results were mainly accounted for by immunocompromised patients. Indeed, if only immunocompetent patients were considered, the sensitivity increased substantially, from 87.1% to 92.5% for Abbott, 87.7% to 91.6% for bioMérieux, 87.1% to 88.8% for DiaSorin, and 74.8% to 83.2% for Bio-Rad (Table 2).

Comparison of the diagnostic efficacies of avidity assays. When comparing the PPVs for acute toxoplasmosis, there was a large variation between kits, ranging from 61.1% for Bio-Rad to 77.5% for bioMérieux (Table 3). In contrast, the NPV was more than 99% for bioMérieux and Bio-Rad but lower for Abbott and Diasorin (95.3% and 96.8%, respectively). These discrepancies resulted in a large variation in the Youden index, which measures the accuracy of the assay, ranging from 0.73 to 0.87. However, the Yule index, measuring the relationship of IgG avidity with acute toxoplasmosis, was acceptable, exceeding 0.9 for all of the assays and ranging from 0.96 to 1 for bioMérieux.

On the other hand, the PPV for latent toxoplasmosis attained the maximum of 100% with all kits, while Yule’s Q coefficient was 1. However, the NPV was lower, ranging from 61.5% for Bio-Rad to 77.8% for bioMérieux. In addition, the Youden index ranged from 0.75 to 0.87 (Table 3).

Distribution of avidity results in the 16 French university and general hospitals. Among the network hospitals, 11 laboratories used bioMérieux assays, 3 Bio-Rad, 2 Abbott, and none DiaSorin. Of 3,885 sera positive for both IgG and IgM, 55.7%
exhibited high avidity, 14.8% intermediate affinity, and 29.5% low avidity (Table 4).

DISCUSSION

A number of different methods have been used to determine the avidity of specific IgG antibodies for dating Toxoplasma infection. The majority of the methods in use for more than 10 years have involved in-house assays based on the use of protein-denaturing agents in washing steps or serum diluents. More recently, assays based on recombinant proteins as blocking agents were introduced (15). The IgG avidity assays have become generally accepted diagnostic tools, with the final goal to exclude recent infection and risk for the fetus, which is crucial in the case of pregnant women with suspected acute infection (e.g., IgM-positive sera). These assays, evaluated using sera from the biobank developed from the French national screening program, have now been

TABLE 1 Comparison of the sensitivities of four IgG avidity immunoassays in 56 patients with acute toxoplasmosis (group 1) according to the classification of equivocal results

<table>
<thead>
<tr>
<th>Assay</th>
<th>Low avidity (%)</th>
<th>High avidity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>100 (56/56)</td>
<td>89.3 (50/56)</td>
</tr>
<tr>
<td>bioMérieux</td>
<td>100 (56/56)</td>
<td>98.2 (55/56)</td>
</tr>
<tr>
<td>Bio-Rad</td>
<td>100 (56/56)</td>
<td>96.4 (54/56)</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>100 (56/56)</td>
<td>94.6 (53/56)</td>
</tr>
</tbody>
</table>

TABLE 2 Comparison of the sensitivities of four IgG avidity immunoassays in patients with latent toxoplasmosis

<table>
<thead>
<tr>
<th>Assay</th>
<th>Group 2 (%)</th>
<th>Group 3 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott</td>
<td>91.7 (77/84)</td>
<td>80 (44/55)</td>
<td>87.1 (121/139)</td>
</tr>
<tr>
<td>bioMérieux</td>
<td>94 (79/84)</td>
<td>78.2 (43/55)</td>
<td>87.7 (122/139)</td>
</tr>
<tr>
<td>Bio-Rad</td>
<td>83.3 (70/84)</td>
<td>61.8 (34/55)</td>
<td>74.8 (104/139)</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>91.7 (77/84)</td>
<td>80 (44/55)</td>
<td>87.1 (121/139)</td>
</tr>
</tbody>
</table>

Immunocompromised patients and treated pregnant women excluded

<table>
<thead>
<tr>
<th>Assay</th>
<th>Group 2 (%)</th>
<th>Group 3 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>95.3 (61/64)</td>
<td>88.4 (38/43)</td>
<td>92.5 (99/107)</td>
</tr>
<tr>
<td>bioMérieux</td>
<td>95.3 (61/64)</td>
<td>86 (37/43)</td>
<td>91.6 (98/107)</td>
</tr>
<tr>
<td>Bio-Rad</td>
<td>92.2 (58/64)</td>
<td>72.1 (31/43)</td>
<td>83.2 (89/107)</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>89.1 (57/64)</td>
<td>88.4 (38/43)</td>
<td>88.8 (95/107)</td>
</tr>
</tbody>
</table>

a Equivocal avidity was considered low avidity.
b Group 2, IgG positive and IgM negative; group 3, IgG and IgM positive.
incorporated in decision algorithms used in national recommendations (4). Today, several commercial IgG avidity assays are available, although few cross-evaluations of their diagnostic performance have been published (11, 16–18).

One of the primary goals of the French National Center for Toxoplasmosis was to evaluate the performance of the commercialized assays used in the French national screening program for congenital toxoplasmosis (19). Therefore, we evaluated four assays, from Abbott, bioMérieux, Bio-Rad, and DiaSorin, which are the most widely used in French biology laboratories and in reference laboratories abroad. These fully automated assays are based on the exclusion of acute infection, with previous expert advice reporting good performance of the assays.

Considering these assays within the recommended use (to exclude acute infection when high-avidity antibodies are present), the PPV for confirming latent toxoplasmosis was 100%. Yule’s Q coefficient was 1, confirming the strong relationship between high avidity and latent toxoplasmosis. In our large retrospective study, in the group of pregnant women with both IgG and IgM anti-Toxoplasma antibodies, 55.7% were considered to have a latent infection with a single test. Therefore, by measuring IgG avidity in a single first sample in nontreated and immunocompetent patients, we were able to confirm a latent infection and to exclude a recent infection (20, 21).

When we used the above-mentioned biobank to compare the performances of the four assays in detecting acute toxoplasmosis, noting that they were not designed for this purpose, the kinetics of IgG maturation had variable performance. Abbott was the most dynamic assay, probably because it is based on recombinant proteins (SAG1 and GRA8). In contrast to the conventional Bio-Rad, DiaSorin, and bioMérieux (denaturing) avidity tests, the avidity competition used in Abbott’s Architect test detects low-avidity IgG by blocking high-avidity IgG in the sample with a soluble recombinant antigen (8).

In general, the kinetics of avidity maturation were similar for all of the assays. The observed decrease in the IgG titers after 12 weeks could be due to the effect of treatment, as all the pregnant women included in this study were treated for acute toxoplasmosis. This could also account for the less dynamic performance of the three “classical” assays based on a native antigen and the conventional denaturing method for determining avidity (22–24).

In the context of off-label use, the performances in detection of acute cases were highly variable. When equivocal results were considered low avidity, all assays reached 100% sensitivity.

FIG 3 IgG avidity results with the four immunoassays in IgG- and IgM-positive sera in latent toxoplasmosis (n = 55). The black squares represent treated or immunocompromised patients; the circles represent the immunocompetent patients. The horizontal lines represent the upper and lower cutoffs of the gray zone for each assay.
of this study on pregnant women demonstrated that acute toxoplasmosis could not be reliably diagnosed based on low IgG avidity alone. Therefore, only the first sample should be considered a reference sample when interpreting avidity results, as after the first determination, all pregnant women were treated with spiramycin according to French recommendations (20, 23). When we considered only the first sample in our group of 56 nontreated pregnant women with acute toxoplasmosis, sensitivity was 100%. Our results also demonstrate that disequilibrium of host-parasite dynamics due to impaired immunity or an anti-Toxoplasma treatment probably results in a delay of IgG maturation. Therefore, results from immunocompromised patients or those treated for Toxoplasma should be interpreted with caution. This is clearly indicated only in the Vidas booklet.

In terms of cost-effectiveness, avidity testing is a powerful tool, allowing optimization of screening and follow-up of pregnant women (25–27). This point is confirmed by our retrospective study among the French network hospitals, which shows that half of the cases with detection of both IgM and IgG antibodies were identified as latent toxoplasmosis, thus avoiding unnecessary subsequent maternal and fetal investigation and treatment. For this reason, the assay price should also be considered. In our study, the

### TABLE 3 Comparison of PPVs, NPVs, Youden indexes, and Yule’s Q coefficients of four IgG avidity immunoassays for patients with acute or latent toxoplasmosis

<table>
<thead>
<tr>
<th>Assay</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Youden index</th>
<th>Yule’s Q coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxoplasmosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott</td>
<td>73.5</td>
<td>95.3</td>
<td>0.76</td>
<td>0.96</td>
</tr>
<tr>
<td>bioMérieux</td>
<td>77.5</td>
<td>99.2</td>
<td>0.87</td>
<td>1</td>
</tr>
<tr>
<td>Bio-Rad</td>
<td>61.1</td>
<td>99.1</td>
<td>0.73</td>
<td>0.99</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>74.3</td>
<td>96.8</td>
<td>0.8</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Latent toxoplasmosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott</td>
<td>100</td>
<td>75.7</td>
<td>0.87</td>
<td>1</td>
</tr>
<tr>
<td>bioMérieux</td>
<td>100</td>
<td>76.7</td>
<td>0.88</td>
<td>1</td>
</tr>
<tr>
<td>Bio-Rad</td>
<td>100</td>
<td>61.5</td>
<td>0.75</td>
<td>1</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>100</td>
<td>75.7</td>
<td>0.87</td>
<td>1</td>
</tr>
</tbody>
</table>

*For the acute-toxoplasmosis population, in an off-label use of the reagents, we estimated the PPV and NPV of a low-avidity result.*

*For the latent-toxoplasmosis population, in an approved use, similar biostatistical results were calculated using the proportion of high-avidity results. For all patients, equivocal or intermediate values were considered false negatives in subjects with acute toxoplasmosis and false positives in subjects with latent toxoplasmosis.*

*The Youden index measures the effectiveness of the test (negative index, ineffective test; index close to 1, effective test).*

*Yule’s Q coefficient measures the relationship to the IgG avidity index (the closer the coefficient is to 1, the stronger the relationship).*
prices for one run of each reagent (not considering external and internal quality control sera) for the determination of IgG avidity were €11.63 for Architect (Abbott), €5.50 for Vidas (bioMérieux), €8.16 for Platelia Toxo IgG Avidity (Bio-Rad), and €6.44 for Liaison (DiaSorin). The cheapest assay, Vidas (bioMérieux), also had the best performance for the diagnosis of latent toxoplasmosis. In any case, avidity testing remains expensive, according to the economic evaluations of Stillwagon et al. (27). Thus, we recommend sending inconclusive sera to an expert laboratory that uses these complementary methods (4). Of interest, the Architect assay, which employs recombinant antigens, provided the best performance for detecting latent infection in the presence of persistent IgM. This means that the use of recombinant antigens for toxoplasmosis, although valid for early antigens (i.e., SAG1 and MAG1) (28), GRA8, and ROP1) mature significantly earlier than those directed against later antigens (i.e., GRA7, IgGs against antigens recognized early (i.e., GRA7, GRA8, and ROP1) mature significantly earlier than those directed against later antigens (i.e., SAG1 and MAG1) (28).

In conclusion, the avidity test provides a rapid means for identifying latent Toxoplasma infection in pregnant women who show both IgG and IgM anti-Toxoplasma antibodies on initial testing during pregnancy. However, there are some limitations in the use of this method. Avidity assays are not conclusive in some immunocompromised patients and those treated for toxoplasmosis. Overall, optimal diagnostic performance is achieved by using appropriate combinations of serological, culture-based, and PCR techniques.

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