Assessing Immunity to Rubella Virus: a Plea for Standardization of IgG (Immuno)assays

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Immunity to rubella virus (RV) is commonly determined by measuring specific immunoglobulin G (RV IgG). However, RV IgG results and their interpretation may vary, depending on the immunoassay, even though most commercial immunoassays (CIAs) have been calibrated against an international standard and results are reported in international units per milliliter. A panel of 322 sera collected from pregnant women that tested negative or equivocal for RV IgG in a prior test (routine screening) was selected. This panel was tested with two reference tests, immunoblotting (IB) and neutralization (NT), and with 8 CIAs widely used in Europe. IB and NT gave concordant results on 267/322 (82.9%) sera. Of these, 85 (26.4%) sera were negative and 182 (56.5%) sera were positive for both tests. All 85 IB/NT-negative samples were classified as negative with all CIAs. Of the 182 IB/NT-positive samples, 25.3 to 61.5% were classified as equivocal and 6 to 64.8% were classified as positive with the CIAs. Wide variations in titers in international units per milliliter were observed. In our series, more than half of the women considered susceptible to RV based on CIA results tested positive for RV antibodies by IB/NT. Our data suggest that (i) sensitivity of CIAs could be increased by considering equivocal results as positive and (ii) the definition of immunity to RV as the 10 IU/ml usual cutoff as well as the use of quantitative results for clinical decisions may warrant reconsideration. A better standardization of CIAs for RV IgG determination is needed.

Rubella is a mild viral disease that typically occurs in childhood. The risks of congenital infection and defects depend on the gestational age at infection. A rubella virus (RV) infection during embryogenesis often leads to the classic triad of cataracts, cardiac abnormalities, and sensorineural deafness, but many other defects may be observed (1). RV was first isolated in 1962 (2, 3) during the 1962-to-1964 rubella pandemic. In the following years, serologic assays were developed (4–6), and in 1969, three rubella vaccines (HPV-77, Cendehill, and RA27/3) were licensed. Selective or universal vaccination programs adopted by some countries led to a tremendous improvement in the control of congenital rubella in the ensuing 50 years, including elimination in the region of the Americas (7). However, elimination has not been achieved elsewhere. For example, the target of one case of congenital rubella syndrome per 100,000 live births by 2015 had to be renewed by the World Health Organization (WHO) Regional Office for Europe. The Global Measles and Rubella Strategic Plan 2012–2020 aims to eliminate measles and rubella in at least five WHO regions by the end of 2020 (8).

In developed countries, women of childbearing age are routinely screened for rubella antibodies to identify and vaccinate susceptible women (9, 10). Expert committees have values for immunity based on the hemagglutination inhibition assay (HAI) set in international units per milliliter, which have proved very useful. However, HAI gave a high level of false-positive reactions and did not easily differentiate between low titers of antibody from nonspecific inhibitors of agglutination (11, 12). Immunity to RV is now commonly determined by measuring rubella virus-specific IgG (RV IgG), usually by commercial immunoassays (CIAs) using enzymatic or chemiluminescent detection systems. These CIAs have often been calibrated with a WHO international standard and report results in international units per milliliter. Currently, cutoff values for immunity are usually set at 10 IU/ml (less frequently at 15 or 20 IU/ml).

However, the use of international units implies that serologic assays are highly standardized and that results obtained by different assays are completely comparable. However, the antigens used in the assays (total virus or recombinant antigens), the conjugate, and the assay format (indirect, sandwich, competition, or capture) differ from one assay to another. Under these conditions, RV IgG quantitative results and their interpretations may be different and even discordant for the same serum, depending on the CIA used. Discrepancies between assays have been confirmed by several studies (13–15) and can have an impact on diagnosis. Indeed, such discrepancies can lead to (i) confused clinical management of pregnant women, (ii) unnecessary revaccinations of already immune individuals, and (iii) reporting of false seroconversions among people with low RV IgG titers. The latter point might ex-
plain why a recent study in Texas reported a high incidence (6.8%) of rubella infection during pregnancy (16). Differences in assay cutoffs and other factors (e.g., antigen used) may also lead to significant differences in the comparability of seroprevalence determinations, which are becoming increasingly used to monitor progress of rubella control activities. Indeed, seroprevalence data for 2013 collected from England, Germany, and France show that the rate of negative or equivocal results for RV IgG is higher in vaccinated populations (personal communications from C. Peckam, United Kingdom, D. Huzly, Germany, and the National Institute of Health [InVS], France). This is not surprising as post-vaccination studies indicate that, although the immune response to vaccination mimics that of wild-type infection, the levels of specific antibodies are lower than after natural infection. In countries that implemented vaccination decades ago, the circulation of RV has decreased significantly and the percentage of individuals who are naturally immune has declined (17). Consequently, these populations have lower levels of RV IgG, and the risk of misclassification of immunity is likely higher given the lack of complete standardization of RV IgG CIAs near the cutoff for immunity. Furthermore, tracing the history of rubella standards is challenging (12) since there is less breakthrough rubella infection for naturally immune or vaccinated persons than for other diseases: e.g., measles, HAI (and subsequently CIA) levels that constitute protection are usually specified by expert committees, rather than studies of breakthrough disease.

To provide objective data concerning the difficulties of assessing rubella immunity using different CIAs, we undertook a study in which a panel of RV IgG equivocal or negative samples collected during routine RV screening in three European countries was tested with 8 RV IgG CIAs, and the results were compared to two reference assays: an immunoblot (IB) and a neutralization (Nt) test. The results of that evaluation are reported here.

**MATERIALS AND METHODS**

**Samples.** A total of 322 serum or plasma samples were included in the study. The samples were collected in France (n = 181), Germany (n = 100), and Italy (n = 41). All samples tested negative or equivocal for RV IgG at screening with the assays commonly used in France (DxI; Beckman Coulter, Brea, CA), Germany (Centaur; Siemens Healthcare, Erlangen, Germany) and Italy (ETI-Rubek-G Plus; DiaSorin, Saluggia, Italy). Samples with equivocal results for RV IgG were included in the panel on the basis that women with these results are considered negative in routine clinical practice. All samples were collected from pregnant women with no recent history of rubella infection (universal screening). Vaccination status was not available.

After initial testing, the samples were stored and transported frozen to the French National Reference Laboratory in Villejuif, France, to the Institute for Virology in Freiburg, Germany, and to the Centers for Disease Control and Prevention (CDC), Atlanta, GA, where they were stored at –20°C until testing.

**Assays.** (i) **Reference assays.** All 322 samples were tested with a commercial IB (recomBlot rubella IgG; Mikrogen GmbH, Neuried, Germany), and a high-throughput-optimized soluble immunocolorimetric neutralization (Nt) assay developed and performed at the CDC.

IB allows detection of RV-specific antibodies required for a reliable serological diagnosis, namely, antivenenvelope (anti-E1 and -E2), anti-capsid (C), and anti-E1/E2 antigen complex antibodies. RV antigens are separated by SDS-PAGE and transferred to a nitrocellulose membrane. The nitrocellulose strip is incubated overnight with the samples diluted 1 in 100 in buffer. RV-specific antibodies present in the sample bind to the RV antigens, forming bands visible on the strip. An IB was scored positive...
TABLE 1 Correlation between RV neutralization and immunoblot (reference assay) results on 322 pretested RV IgG-negative or equivocal serum samples

<table>
<thead>
<tr>
<th>No. (%) of samples tested positive [IU/ml range]</th>
<th>Architect (Abbott Diagnostics)</th>
<th>Cobas 6000 (Roche Diagnostics)</th>
<th>Vidas (bioMérieux)</th>
<th>Enzygnost (Siemens Healthcare)</th>
<th>LXL (DiaSorin)</th>
<th>Serion</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB/Nt positive</td>
<td>11 (6.0) [100–141]</td>
<td>109 (59.9) [10–500]</td>
<td>65 (35.7) [13–27]</td>
<td>15 (8.2) [15.0–22.8]</td>
<td>115 (63.2) [10.0–66.8]</td>
<td>46 (26.4) [10–99]</td>
</tr>
<tr>
<td>IB/Nt negative</td>
<td>85 (100) [0–0]</td>
<td>85 (100) [0–0]</td>
<td>85 (100) [0–0]</td>
<td>85 (100) [0–0]</td>
<td>85 (100) [0–0]</td>
<td>85 (100) [0–0]</td>
</tr>
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</table>

When at least the anti-E1 band was observed. An IB was scored negative if no bands were observed. IB testing was performed at the French National Reference Laboratory.

RV-specific neutralizing antibodies were measured using the previously described Nt assay (18). Briefly, samples were diluted in a 2-fold series (in duplicate), mixed with a known amount of RV (HPV77), and incubated at 37°C in 5% CO2 for 90 min. Each test run included positive and negative serum controls, virus controls (no serum), and uninfected controls (no serum or virus). Serum-virus mixtures and controls were transferred to Vero cell monolayers grown in a 96-well microplate and incubated for 60 min. Overlay medium was added to each well, and microplates were incubated for 3 days. Cells were then fixed with cold methanol, and a soluble immunocolorimetric assay was performed using E1 monoclonal antibody and anti-mouse horseradish peroxidase-conjugated secondary antibody. The optical density (OD) of each well was determined with a spectrophotometer. The RV Nt titer was defined as the reciprocal of the last dilution that reduced the virus control OD by at least 50%. We considered Nt positive to be a titer of ≥10 and Nt negative to be a titer of <10. Nt was performed blindly with respect to IB results.

IB has been recently used as the standard for a study of CIAs (19). Although Nt is the standard assay for defining immunity for some diseases (e.g., measles), RV Nt titers sufficient for protection have not been determined. Thus, in order to define positive and negative RV antibody status stringently for the present study, only samples with concordant IB/Nt results were considered with respect to CIA results.

(ii) CIAs. All 322 samples were tested with 8 CIAs according to the manufacturer’s instructions. The characteristics of the following 8 CIAs evaluated are listed in Table 1: Architect rubella IgG (Abbott Diagnostics, Abbott Park, IL), Cobas 6000 rubella IgG (Roche Diagnostics, Mannheim, Germany), Vidas Rub IgG II (bioMérieux, France), DxI rubella IgG (Beckman Coulter, Brea, CA), Centaur RubG (Siemens Healthcare, Erlangen, Germany), Enzygnost anti-rubella virus IgG (Siemens Healthcare, LXL rubella IgG (DiaSorin, Saluggia, Italy), and Serion enzyme-linked immunosorbent assay (ELISA) rubella virus IgG (Institut Virion/Serion, GmbH, Würzburg, Germany). All assays report results in international units per milliliter. These assays are widely used in Europe and have mostly (7/8) recently been evaluated for overall performance (19). The cutoff values chosen for the analysis of results are those recommended for the manufacturer. The French National Reference Laboratory did testing using the DxI, Architect, Vidas, Enzygnost, LXL, and Cobas 6000 assays, and the Institute for Virology in Freiburg (Germany) did testing using the Centaur and Serion assays.

RESULTS

Definition of serologic status against rubella according to reference assays. Ninety-four out of 322 samples (29.2%) were found negative by Nt. Among those, 85 were also negative by IB. Two hundred twenty-eight samples (70.8%) were found positive by Nt. Among those, 85 were also positive by IB. Of the 55 discrepant samples, 9 were Nt negative but IB positive, and 46 were Nt positive but IB negative (Table 2). When IB was negative but Nt pos-

TABLE 2 Correlation between RV neutralization and immunoblot (reference assay) results on 322 pretested RV IgG-negative or equivocal serum samples

<table>
<thead>
<tr>
<th>No. (%) of samples</th>
<th>Nt negative</th>
<th>Nt positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB negative</td>
<td>85 (26.4) a</td>
<td>46 (14.3)</td>
<td>131 (40.7)</td>
</tr>
<tr>
<td>IB positive</td>
<td>9 (2.8)</td>
<td>182 (56.5) b</td>
<td>191 (59.3)</td>
</tr>
<tr>
<td>Total</td>
<td>94 (29.2)</td>
<td>228 (70.8)</td>
<td>322 (100)</td>
</tr>
</tbody>
</table>

a Concordant negative samples were defined as best negative samples. 
b Concordant positive samples were defined as best positive samples.
Table 4 Five representative IB/Nt-positive samples (among the 182 best positives) giving discrepant interpretation of results, depending on the commercial immunoassay used

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Architect (Abbott Diagnostics)</th>
<th>Cobas 6000 (Roche Diagnostics)</th>
<th>Vidas (bioMérieux)</th>
<th>DxI (Beckman Coulter)</th>
<th>Centaur (Siemens Healthcare)</th>
<th>Enzygnost (Siemens Healthcare)</th>
<th>LXL (DiaSorin)</th>
<th>Serion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (E)</td>
<td>60.4 (P)</td>
<td>10 (E)</td>
<td>9.4 (N)</td>
<td>10.7 (P)</td>
<td>6 (E)</td>
<td>3.5 (N)</td>
<td>8.11 (N)</td>
</tr>
<tr>
<td>2</td>
<td>7 (E)</td>
<td>&gt;500 (P)</td>
<td>10 (E)</td>
<td>12.2 (E)</td>
<td>14.1 (P)</td>
<td>13 (P)</td>
<td>4.9 (N)</td>
<td>10.8 (E)</td>
</tr>
<tr>
<td>3</td>
<td>4.5 (N)</td>
<td>61.8 (P)</td>
<td>7 (N)</td>
<td>11.4 (E)</td>
<td>4.8 (N)</td>
<td>7 (P)</td>
<td>3.2 (N)</td>
<td>5.5 (N)</td>
</tr>
<tr>
<td>4</td>
<td>8.9 (E)</td>
<td>6.5 (N)</td>
<td>20 (P)</td>
<td>11.2 (E)</td>
<td>33.3 (P)</td>
<td>14 (P)</td>
<td>16.9 (P)</td>
<td>21.4 (P)</td>
</tr>
<tr>
<td>5</td>
<td>10.7 (P)</td>
<td>9.5 (N)</td>
<td>22 (P)</td>
<td>14.4 (E)</td>
<td>38.5 (P)</td>
<td>14 (P)</td>
<td>23.2 (P)</td>
<td>36.9 (P)</td>
</tr>
</tbody>
</table>

a P, positive; E, equivocal; N, negative.

Table 5 Concordance between Nt/IB and CIA results from the 85 best RV antibody-negative and 182 best RV antibody-positive serum samples according to different interpretation of RV IgG CIA equivocal results

<table>
<thead>
<tr>
<th>Interpretation of CIA equivocal results</th>
<th>Architect (Abbott Diagnostics)</th>
<th>Cobas 6000 (Roche Diagnostics)</th>
<th>Vidas (bioMérieux)</th>
<th>DxI (Beckman Coulter)</th>
<th>Centaur (Siemens Healthcare)</th>
<th>Enzygnost (Siemens Healthcare)</th>
<th>LXL (DiaSorin)</th>
<th>Serion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered negative</td>
<td>96 (36)</td>
<td>194 (72.7)</td>
<td>150 (56.2)</td>
<td>100 (37.5)</td>
<td>200 (74.9)</td>
<td>203 (76.0)</td>
<td>117 (43.8)</td>
<td>107 (40.1)</td>
</tr>
<tr>
<td>Considered positive</td>
<td>202 (75.7)</td>
<td>194 (72.7)</td>
<td>206 (77.2)</td>
<td>212 (79.4)</td>
<td>248 (92.9)</td>
<td>249 (93.3)</td>
<td>200 (74.9)</td>
<td>195 (73.0)</td>
</tr>
</tbody>
</table>

a The Cobas 6000 RV IgG assay has no equivocal zone.

Itivitive, neutralizing titers ranged from 10 to 80. IB/Nt discordant samples were retested by IB, but results did not change. No retesting was done for Nt because sera had already been tested in duplicates.

In the absence of true RV-negative samples (i.e., sera from individuals who have never been infected by or vaccinated against RV) and true RV-positive samples (i.e., sera from definitely immune individuals), the 85 discordant IB/Nt-negative sera and the 182 discordant IB/Nt-positive sera were considered the best negative and the best positive sera, respectively, that could be defined in this study.

Performance of 8 CIAs. All 322 samples were tested with 8 CIAs. However, the performance of each CIA was evaluated only on the 85 IB/Nt-negative (best negative) and 182 IB/Nt-positive (best positive) samples. Qualitative and quantitative results observed with CIAs for the 267 IB/Nt concordant samples are summarized in Table 3.

All 85 IB/Nt-negative samples were scored negative with all 8 CIAs (100% specificity). Among the 182 IB/Nt-positive samples, 176 (96.7%) tested positive or equivocal by at least one CIA, although none gave concordant positive results by all assays. In detail, 106 (58.2%) samples gave a positive result by at least one CIA and a negative result by one or more CIAs, and 101 (55.5%) samples gave at least three possible interpretations (negative/equivocal/positive) (data not shown).

As for RV IgG titers, the 8 CIAs included in this study report results in international units per milliliter, and values below the cutoff are also shown in Table 3. Titers of best positives expressed results in international units per milliliter ranged from 0.4 to 14.8 with the Architect assay, from 0 to >500 with the Cobas 6000 assay, from 2 to 27 with the Vidas assay, from 1.3 to 22.8 with the DxI assay; from 0.2 to 66.8 with the Centaur assay, from 2 to 27 with the Vidas assay, from <3 to 23.2 with the LXL assay, and from 2.3 to 36.9 with the Serion assay. Moreover, we observed major differences in RV-IgG titers (up to a factor of 10) between these assays for the same best positive sample, as exemplified in Table 4.

Concordance between IB/Nt and CIA qualitative results. Concordance of the serologic status determined by IB/Nt with qualitative test results (positive, equivocal, or negative) of the CIAs varied greatly, depending on the interpretation of the CIA’s equivocal results. In fact, as shown in Table 5, if the equivocal results are considered to be negative for RV IgG (according to the current management of pregnant women), the concordance is quite poor (36.0 to 76.0%), depending on the CIA. However, if the equivocal results are considered positive, concordance increases, ranging from 73.0 to 93.3%, without losing specificity.

Discussion

Recent data from England, France, Germany, and Australia showed that in the younger age groups, rubella IgG levels are lower than those in older populations because rubella immunity is mostly vaccine induced in the former group and natural boosters are now less likely to occur due to the increasing vaccination coverage for children and consequently the low incidence of natural rubella infection in the community (17; personal communications from C. Peckam, United Kingdom, D. Huzly, Germany, and the National Institute of Health [InVVS], France). In addition, the share of the vaccinated population showing equivocal or negative results and, therefore, considered susceptible is growing. These individuals may be unnecessarily vaccinated or revaccinated, and, moreover, in laboratories using CIAs with nonequivalent sensitivities and specificities, an incorrect determination of a rise in rubella IgG titers might occur, leading to a diagnosis of rubella, a diagnosis of great significance to a pregnant woman. The disparities between the results obtained with different immunoassays emphasize the importance of using the same rubella IgG assay throughout pregnancy and testing paired sera in parallel.

Given the difficulties faced in clinical practice when discordant
results are observed in pregnant women with low RV IgG titers, we chose to collect a panel of sera negative or equivocal for RV IgG with CIAs collected from such women in order to (i) explore how to improve discrimination between immune and nonimmune pregnant women without an available vaccination history and (ii) to evaluate the standardization between RV IgG CIAs.

The presence or absence of RV-specific antibody in sera used in this study was defined as a concordant result obtained with IB and Nt. In this respect, considering the inherent differences between IB and the Nt assay, it is important to underline that the overwhelming majority of sera (82.9%) gave either negative or positive concordant results. Discordant results may be explained on the basis that the IB assay primarily detects anti-E1 IgG antibodies and is considered to be more specific than sensitive, whereas Nt allows assessment of the biological function of antibodies and detects other classes of antibodies (e.g., IgM and IgA). Thus, the fact that IB and Nt detect RV-specific antibodies with different antigenic specificities and functional activities was exploited in order to stringently characterize the panel of sera used to assess performance of CIAs for RV immunity determination.

The first important result of this study is that 56.5% of the women considered susceptible at RV prenatal screening were in fact RV seropositive according to both IB and Nt. Since such individuals have strong evidence of previous exposure to RV according to IB and the Nt assay (most likely due to vaccination), their immune status may need to be evaluated differently than prescribed by assay interpretations based on immunity thresholds in international units per milliliter. Some clinical decisions—for example, revaccination—might be unnecessary for these individuals. Studies specifically addressing this issue are needed.

After defining RV immune status using Nt/IB concordant samples, we studied the sensitivities and specificities of 8 CIAs widely used in Europe. These performances were evaluated with a stringently selected panel of low-positive and negative samples that currently represent 5 to 10% of the samples tested for rubella IgG in our lab and are therefore not representative of the assays’ characteristics in the general population. Specificity was 100% for all assays, whereas sensitivity ranged from 6 to 64.8%, even if each CIA reports results in international units per milliliter. A number of reasons might explain the difference in sensitivities. First, although an international reference standard has been available since the 1980s and has been widely used by manufacturers to calibrate their assays for RV IgG detection and quantification, our study, along with others (13–15), shows that this has not resulted in proper standardization of CIAs. Indeed, the “minimum immune titer” of 10 IU/ml was established mainly using data from HAI assays (widely used in the 1980s but no longer a common diagnostic test) and was defined as the titer securely above any nonspecific reactions, which are problematic for HAI assays (11). In addition, from early on, manufacturers relied heavily on the single international standard available at the time of assay development and used the “minimum immune titer” of 10 IU/ml. Finally, the characteristics of the 8 CIAs used in the present study are very different as far as solid phase, platform, antigen, detection system, standard, and range of interpretation of results are concerned, and this could also be a reason for the observed discrepancies.

Seven of the 8 CIAs investigated in the present study include an equivocal zone in the interpretation of results. If the equivocal results were considered RV IgG negative (according to the current management of pregnant women), the concordance with Nt/IB was quite poor: 36.0 to 76.0%, depending on the assay. On the other hand, if the equivocal results obtained by CIAs were considered positive, concordance with the assigned status improved, ranging from 73.0 to 93.3% without losing specificity (Table 5). Therefore, for the set of sera used in this study, removing the equivocal zone for each CIA appeared highly beneficial in terms of concordance with reference assays. However, since these sera were selected to be near the cutoff, the improvements seen here may not be as significant for serum sets selected differently.

Focusing on the RV IgG titer of the best positive (Nt/IB positive) samples giving “false-negative” results by different CIAs, we suggest that evaluation of lower cutoff values for each CIA in immune determination algorithms would be useful. This suggestion is in recognition of the potential implications for clinical management of results near the current cutoff, especially during serological follow-up of pregnant women. The remaining discordant results involve only a few samples that are negative with CIAs and positive with Nt and IB. From a practical point of view, these negative results are not an issue because it is more acceptable to report a false-negative RV-IgG result (resulting in unnecessary vaccinations) than a false-positive one.

Having a single cutoff (10 IU/ml) for CIAs may not be the best practice. Expert committees have been the source of standards for defining immunity to RV (12). Although use of a single standard to establish cutoffs for CIA is common, our study, along with previous ones, shows that establishing new CIA cutoffs could improve qualitative correlation between assays. In order to contribute to this better standardization of rubella IgG CIAs, a panel of confirmed negative rubella IgG samples would be useful to establish assay-specific cutoffs. Expert committees on establishing rubella immunity might consider additional guidance for results near or below the immunity cutoff (20). Finally, this study could help companies recalibrate their assay by providing a stringent approach to the definition of true negatives and positives.

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