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SUMMARY OF SAFETY AND EFFECTIVENESS

RUBELLA IgG METHOD FOR THE IMMUNO 1[®] SYSTEM

Listed below are comparisons of the performance between the Immuno 1 Rubella IgG method (T01-3547-51) and similar devices that were granted FDA determination of substantial equivalence: the Sanofi Platelia Rubella IgG kit and the Abbott IMx Rubella IgG assay. The comparative data with the Sanofi Platelia assay was collected in-house at Miles Inc. on two manufactured lots of reagents. The comparative data with the Abbott IMx assay was collected at two outside clinical sites using two additional lots of manufactured reagents. All HAI testing was done by a state health agency reference laboratory

The information used in this Summary of Safety and Effectiveness was extracted from the Rubella IgG method sheet and from data on file at Miles Inc. A report provided by the CDC for results obtained with the Immuno 1 Rubella IgG method for the CDC Rubella serum panel is attached as Appendix 1.

INTENDED USE

This *in vitro* diagnostic method is intended to quantitatively measure Rubella IgG in human serum on the *Technicon Immuno 1[®]* System. Measurements of Rubella IgG are designed to aid in the determination of immune status by detecting IgG class antibodies to rubella virus in human sera. The method is not intended for use on any other system.

CHARACTERISTICS

The assay has a range of 0 to 500 IU/mL. Six calibrators are used with values of 0, 10, 20, 50, 200, 500 IU/mL, traceable to the WHO 2nd International Standard for Anti-Rubella Serum. Agreement between Immuno 1[®] Rubella IgG Calibrators and a set of calibrators prepared with the WHO Standard is shown in Figure 1 with regression analysis.

IMMUNO 1 vs WHO Rubella IgG Calibrators

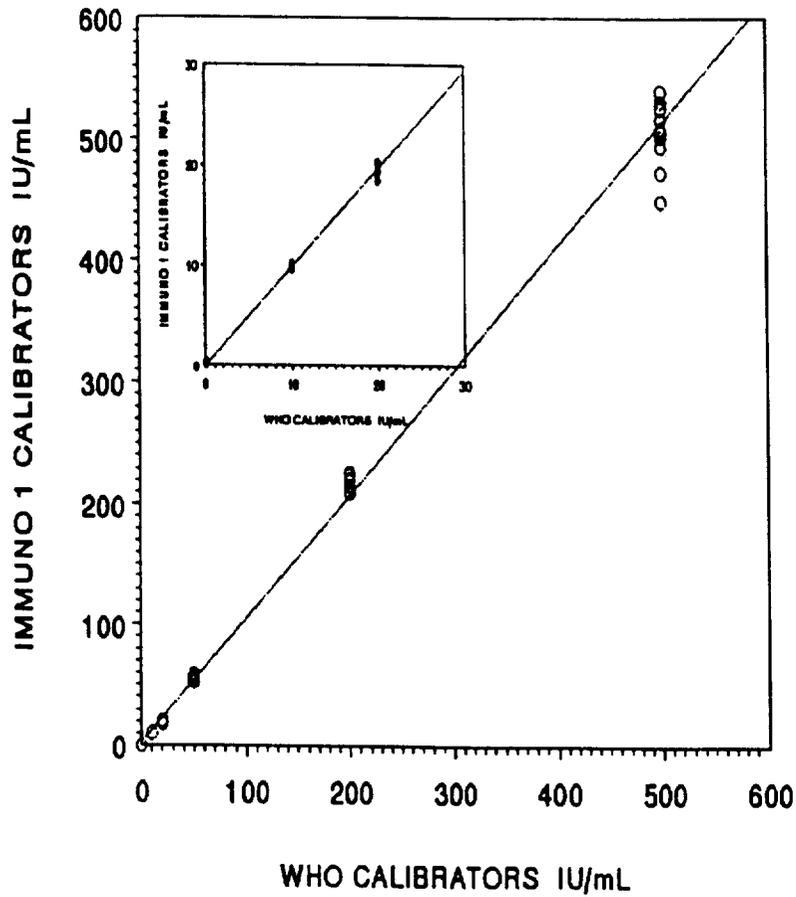


Figure 1. Correlation between Immuno 1 Rubella IgG calibrators and the WHO International Standard. Ten replicate measurement were made at each calibrator level.

Linear regression analysis yielded the following results:

$$Y = 1.020 X + 2.984$$

$$R = 0.9989$$

$$95\% \text{ CI intercept} = 2.984 \pm 3.781$$

$$95\% \text{ CI slope} = 1.020 \pm 0.017$$

Cut-off Value Selection

The cutoff value is 10 IU/mL, based on recommendations of the NCCLS and the CDC. Accordingly, the NCCLS subcommittee "... recommends the use of 10 IU/mL as an indicator of immune status. This breakpoint detects most seropositive persons. Because detection of nonimmune status is clinically more important, selecting 10 IU/mL as the indicator of immune status favors immunization." The assay is calibrated against the WHO 2nd International Rubella IgG standard. The validity of using 10 IU/mL as the cut-off in the Immuno 1 Rubella IgG assay is demonstrated by the comparative clinical performance, Table 3, and summarized by the receiver-operator-curve analysis (ROC) shown in Figures 2a thru 2f and Table 4 of this report. A report provided by Dr. John Stewart, VEH Branch of the CDC in Atlanta, shows that the Immuno-1 Rubella IgG method correctly classified all of the CDC Rubella proficiency panel samples (Appendix 1).

IMPRECISION

Imprecision claims for the IMMUNO 1[®] Rubella IgG method are based on data collected at two independent clinical site studies. Results are summarized in Table 1. These estimates of imprecision were obtained from replicate assays of human serum pools, controls, and calibrators. Imprecision estimates were collected and computed according to NCCLS document EP5-T2, *User Evaluation of Precision Performance of Clinical Chemistry Devices; Tentative Guideline*. On-board reagent and calibration stability claims are 60 and 30 days, respectively. Calibration stability requires recovery of target values within ± 2 standard deviations of the claimed level specific total standard deviations.

Table 1. Imprecision of Immuno 1 Rubella IgG Method

LEVEL (IU/mL)	SD TOTAL (IU/mL)	CV TOTAL (%)	SD WITHIN-RUN (IU/mL)	CV WITHIN-RUN (%)
10	0.7	7.1	0.5	5.5
20	1.5	7.5	1.4	7.2
200	13.4	6.7	10.1	5.0

METHOD COMPARISONS

Comparative results to the Abbott IMx were collected from two clinical sites, each using two lots of Immuno 1 Rubella IgG manufactured reagents. The Pasteur Diagnostics Platelia results were obtained in-house also, using two lots of manufactured reagents different from those used at the clinical sites. Thus a total of four manufactured reagent lots are represented in the method comparisons.

Sensitivity and Specificity

Sensitivity and specificity results, relative to the Sanofi Platelia and the Abbott IMx Rubella IgG assays, are presented in Table 2. The Platelia results were generated on 719 clinical samples (520 from Michigan Department of Public Health and the remaining purchased from an outside vendor, Boston Biomedica, in order to increase the number of negative samples). The sample IU/mL distributions for the in-house and two clinical sites analyses are given in Table 2. The additional negative samples were supplied to the clinical sites as masked specimens.

Table 2. Distribution of Serum Immuno 1 Rubella IgG values.

IU/mL Range	IN-HOUSE		SITE 1		SITE 2	
	No. Smpls	% Total	No. Smpls	% Total	No. Smpls	% Total
0 to < 10	242	33.7	80	27.0	69	24.0
10 to < 20	100	13.9	25	8.4	41	14.3
20 to < 40	95	13.2	32	10.8	65	22.6
40 to < 60	55	7.6	25	8.4	36	12.5
60 to < 100	59	8.2	32	10.8	21	7.3
100 to < 300	135	18.8	83	28.0	48	16.7
300 to < 500	19	2.6	12	4.1	7	2.4
≥500	14	1.9	7	2.4	0	0
Total	719	100	296	100	287	100

Table 3. Immuno 1 Rubella IgG Relative Sensitivity and Relative Specificity in comparison to Sanofi Platelia and Abbott IMx Rubella IgG assays. The Platelia data was collected in-house. IMx data was collected at two outside clinical laboratories. Results are calculated using 10 IU/mL as the cut-off point. The 95% confidence intervals for relative sensitivity and relative specificity were calculated as plus/minus 1.96 times the square root of $p(1-p)/n$ where p is the sensitivity (or specificity) and n is the sample size. The lower 95% confidence interval limit for 100% values are approximated using 99%. Overall agreement (OA) is the percentage of correct results. Discrepant samples were analyzed by HAI and the results used for resolution.

Miles Inc., Elkhart, IN

	UNRESOLVED PLATELIA					HAI RESOLVED PLATELIA				
	Pos	Neg	Sen (%)	Spec (%)	OA (%)	Pos	Neg	Sen (%)	Spec (%)	OA (%)
Immuno 1 Pos	478	3	83.6±3.0			480	1	96.6±1.8		
Lot Exp1 Neg	94	144		98.0±2.3	86.5	17	221		99.5±0.9	97.5
Immuno 1 Pos	475	2	83.0±3.1			476	1	96.2±1.7		
Lot Exp2 Neg	97	145		98.6±1.9	86.4	19	223		99.6±0.8	97.2

Site 1: NC Baptist Hospital, Winston-Salem, NC

	UNRESOLVED IMx					HAI RESOLVED IMx				
	Pos	Neg	Sen (%)	Spec (%)	OA (%)	Pos	Neg	Sen (%)	Spec (%)	OA (%)
Immuno 1 Pos	216	0	85.7±4.7			216	0	94.3±3.1		
Lot RCG Neg	36	46		100±2.2	87.9	13	69		100±2.2	95.6
Immuno 1 Pos	218	0	86.5±4.5			218	0	94.8±3.1		
Lot RDG Neg	34	46		100±2.2	88.6	12	68		100±2.2	96.0

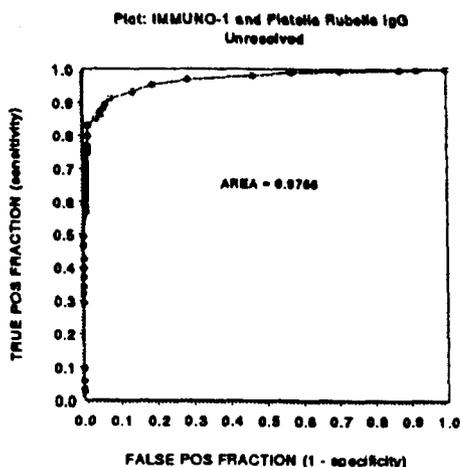
Site 2: Huntsville Hospital, Huntsville, AL

	UNRESOLVED IMx					HAI RESOLVED IMx				
	Pos	Neg	Sen (%)	Spec (%)	OA (%)	Pos	Neg	Sen (%)	Spec (%)	OA (%)
Immuno 1 Pos	217	0	88.2±4.3			217	0	98.2±1.8		
Lot RCG Neg	29	45		100±2.3	90.0	4	70		100±2.3	98.6
Immuno 1 Pos	219	0	89.0±4.1			219	0	98.2±1.8		
Lot RDG Neg	27	45		100±2.3	90.7	4	68		100±2.3	98.6

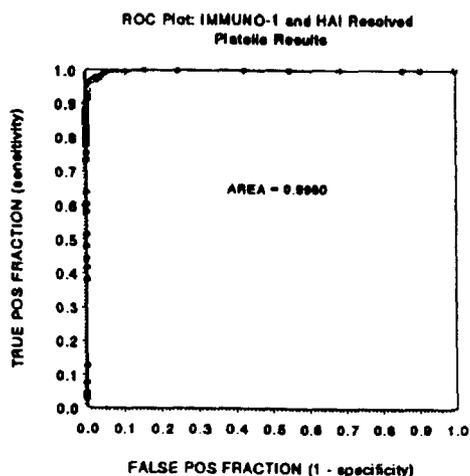
Receiver-Operating Characteristic (ROC) Analysis

The area under the ROC plot is used to estimate the diagnostic accuracy of the Immuno 1 Rubella IgG assay relative to Platelia and IMx Rubella IgG assays. ROC plots before and after HAI resolution, are shown in figure 2 a-f. The ROC plot areas are reported in Table 4. ROC plots were constructed and analyzed according to NCCLS Document GP10-T (1993) "Assessment of the Clinical Accuracy of the Laboratory Tests Using Receiver Operating Characteristics (ROC) Plots; Tentative Guideline".

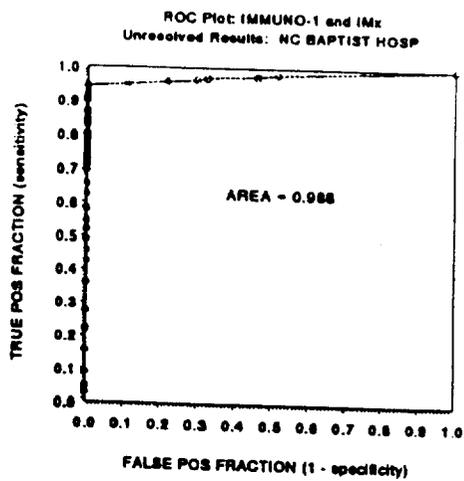
Figure 2. ROC Plots. (a,b) In-House with Immuno 1 and the Platelia Rubella IgG assays. (c,d) Site 1 data for Immuno 1 and the IMx Rubella IgG assays, and (e,f) Site 2 data for Immuno 1 and the IMx Rubella IgG assays .



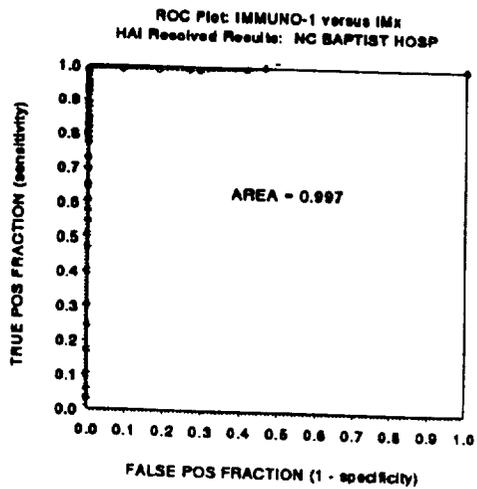
(a) Unresolved In-house Immuno 1 and Platelia Results (Area = 0.9766)



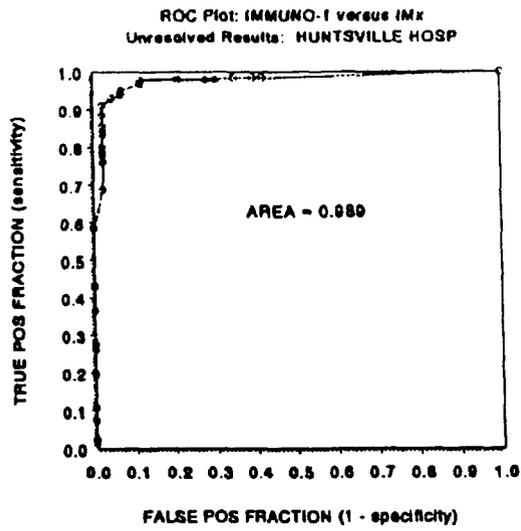
(b) HAI Resolved In-house Immuno 1 and Platelia Results (Area = 0.9980)



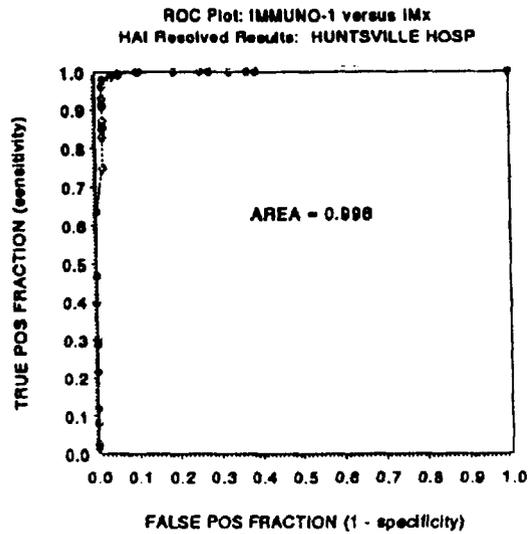
(c) Unresolved Immuno 1 versus IMx, NC Baptist Hospital Area = 0.988



(d) Resolved Immuno 1 versus IMx, NC Baptist Hospital Area = 0.997



(e) Unresolved Immuno 1 versus IMx, Huntsville Hospital, Area = 0.989



(f) Resolved Immuno 1 versus IMx, Huntsville Hospital Area = 0.996

Table 4. ROC Plot Areas

SITE	Comparative Method	Unresolved ROC Area	HAI Resolved ROC Area
Miles Inc.	Platelia	0.976	0.998
NC Baptist Hosp	IMx	0.988	0.997
Huntsville Hosp	IMx	0.989	0.996

Reproducibility

The classification agreement or reproducibility between duplicate results for the various reagent lots tested is presented in Table 5. The titer distribution of the sample population used in the replicate analysis for rubella IgG Exp 1 and Exp 2 reagent lots was selected in order to meet the NCCLS guidelines for reproducibility of replicate testing and is shown in Table 6. The titer distribution for the clinical site sample populations is given in Table 1.

Table 5. Reproducibility of replicate results.

Miles In House			Replicate 2		Overall Agreement (%)
			Pos	Neg	
Exp 1 Lot	Replicate 1	Pos	158	1	99.5
		Neg	0	41	
Exp 2 Lot	Replicate 1	Pos	158	0	99.5
		Neg	1	41	
NC Baptist Hospital					
RCG Lot	Replicate 1	Pos	214	2	99.0
		Neg	1	79	
RDG Lot	Replicate 1	Pos	217	1	98.7
		Neg	3	75	
Huntsville Hospital					
RCG Lot	Replicate 1	Pos	215	2	99.0
		Neg	1	68	
RDG Lot	Replicate 1	Pos	214	3	98.2
		Neg	2	65	

Table 6. Titre distribution of the in-house sample set used to measure reproducibility for Exp 1 & 2 Rubella IgG Reagent Lots in Table 5 above.

IU/mL Range	Number of Samples	% Total
< 10	41	20.5
10 to < 20	63	31.5
20 to < 40	20	10.0
40 to < 60	11	5.5
60 to < 100	49	24.5
≥ 100	16	8.0
Total	200	100

RESULTS

Samples with results <10 IU/mL are considered negative for the presence of rubella IgG antibodies. Samples with results greater than or equal to 10 IU/mL are considered positive for the presence of IgG antibody to rubella.

The results reported by the laboratory to the physician should include the following statement: "The following results were obtained with the Technicon Immuno 1® Rubella IgG antibody test. IgG values obtained with different manufacturer assay methods may not be used interchangeably. The magnitude of the reported IgG level cannot be correlated to an endpoint titer."

INTERFERENCES

The use of hemolyzed (up to 1000 mg/dL of hemoglobin), lipemic (up to 900 mg/dL of triglycerides) or icteric (up to 25 mg/dL of total bilirubin) samples have no clinically significant effect on method performance, Table 7. Patient samples containing rheumatoid factor, antibodies to Epstein-Barr virus, cytomegalovirus, varicella zoster virus, Herpes Type I virus, Herpes Type II virus and rubeola (measles) virus produced no false positive results in comparison to the Sanofi Platelia method.

TABLE 7 INTERFERING SUBSTANCES

CHOLESTEROL				TRIGLYCERIDE			
mg/dL	IU/mL RUB IgG	% CV	% BIAS	mg/dL	IU/mL RUB IgG	% CV	% BIAS
50	10.98	1.54	-0.09	225	10.59	3.38	-16.88
0	10.99	1.29		0	12.74	2.75	
100	10.10	6.34	0.10	450	12.03	2.55	-4.60
0	10.09	3.17		0	12.61	0.46	
300	7.82	1.31	2.09	675	11.23	1.72	-7.80
0	7.66	2.75		0	12.18	1.61	
400	6.88	2.94	-0.29	900	11.20	1.25	-9.39
0	6.90	2.84		0	12.36	0.64	

HEMOGLOBIN**BILIRUBIN**

mg/dL	IU/mL RUB IgG	% CV	% BIAS	mg/dL	IU/mL RUB IgG	% CV	% BIAS
250	11.96	1.72	-1.64	6.25	12.82	1.29	4.74
0	12.16	1.34		0	12.24	1.50	
500	11.01	1.60	3.28	12.5	12.46	2.81	-0.16
0	10.66	1.26		0	12.48	3.49	
750	10.35	2.56	2.58	18.75	12.13	2.47	3.50
0	10.09	1.79		0	11.72	1.45	
1000	8.85	2.39	8.99	25	11.28	1.41	-0.09
0	8.12	5.21		0	11.29	1.13	