Rubella dilemma: are patients being immunised unnecessarily?

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Introduction

Rubella is an RNA virus that causes a mild infectious disease with an incubation period of 14 to 21 days. Primary infection during the first eight to ten weeks of pregnancy can result in foetal damage in up to 90% of infants. Rubella is a vaccine preventable disease and immunisation for pre-pubertal and non-immune females was introduced in the UK in 1970. A universal rubella immunisation programme was implemented in 1988 with the introduction of the MMR vaccine.

UK NEQAS for Microbiology introduced the Rubella IgG serology EQA scheme in 1979. Two panels each of six specimens, derived from single serum donations, are sent out annually. Although quantitative results are collected and presented in the distribution report, participants are scored on the qualitative interpretation of their results. Specimens with quantitative values that are close to 10 IU/mL are included in the distributions however participants' performance with these specimens is not scored.

Aim

To analyse the variability of qualitative results by method for the detection of low positive specimens (between 5 IU/mL and 15 IU/mL) in the rubella IgG serology EQA scheme.

Methods

- From 2002 to 2006, fifty-four specimens have been distributed.
- Forty-three of the 54 specimens were scored: 11 specimens were negative and 32 were positive.
- Eleven of the 54 specimens were not scored as results from pre-distribution testing gave quantitative values between 5 IU/mL and 15 IU/mL.
- Results reported by participants for these specimens were analysed to determine whether any kits consistently gave results that were excessively high or low.

Results

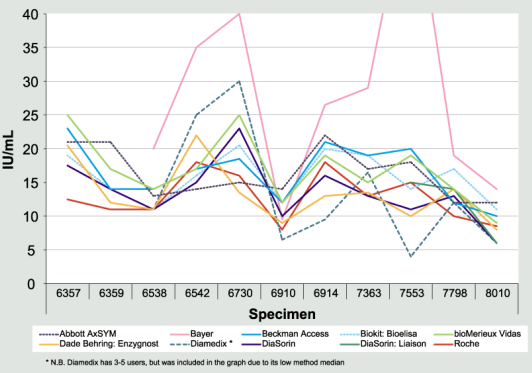
- Participants performance for the 43 scored specimens was good with success rates of 93% to 100% (data not shown):
  - the overall false negative rate was 46/10929 (0.42%),
  - the overall false positive rate was 65/3763 (1.73%).
- For the low positive, non-scored specimens 56.2% to 98.7% of participants reported a positive (>10 IU/mL) result (table 1):
  - 3694/4062 (90.9%) of participants reported their overall result as >10 IU/mL (some participants performed more than one test on specimens with low levels of antibody),
  - 368/4062 (9.1%) of participants reported <10 IU/mL.
- The most popular methods (figure 1) used to detect rubella IgG were:
  - Abbott AxSYM (112-128 users),
  - bioMerieux Vidas (40-58 users),
  - Biokit: Bioelisa (27-38 users),
  - DiaSorin (18-39 users).
- For 8/11 non-scored specimens the Bayer method gave the highest median results (median range: 9.5 to 61) out of those methods with ≥10 users (figure 2).
- For 5/11 non-scored specimens the Roche method gave the lowest or joint lowest median results (median range: 8 to 18).
- For specimen 8010, 209/372 (56.2%) participants reported their result as >10 IU/mL. Eight of the 17 methods used to test this specimen gave medians values ≥10 IU/mL (figure 3).
- Of the 36 different methods used (including those that gave non-numerical data sets), 25 methods had been used to analyse 10 or more of the specimens.
  - Analysis of these 25 methods using ANOVA showed there was strong evidence that not all methods produced the same results ($p<0.001$).
  - Linear regression, taking DiaSorin as the baseline (due to its fairly low mean and large-enough frequency of usage), showed that Bayer produced the highest results (2.1 fold > DiaSorin, 95% CI (2.0-2.3)).
  - Overall Roche followed by Diamedix and DiaSorin produced the lowest results. However there was no evidence of any differences between the 3 methods.

Table 1: Summary of low-positive, 'not scored' specimen details

Year	Specimen no.	Intended result	No. reporting	No. reporting positive (>10 IU/mL)	% reporting positive	No. reporting negative (<10 IU/mL)	No. numerical data sets	Range	Median for all kits	5% CI	95% CI
2002-2003	6357	Rubella IgG positive (>10 IU/mL)	372	363	97.6%	9	329	0-70	21	12	29
2002-2003	6359	Rubella IgG positive (>10 IU/mL)	373	353	94.6%	20	332	0-147	17	10	26
2002-2003	6538	Rubella IgG positive (>10 IU/mL)	366	333	91.0%	33	342	2-118	13	9	19
2002-2003	6542	Rubella IgG positive (>10 IU/mL)	369	364	98.6%	5	339	7-71	16	11	25
2003-2004	6730	Rubella IgG positive (>10 IU/ml)	370	365	98.7%	5	344	0-55	18	12	33
2003-2004	6910	Rubella IgG positive (>10 IU/ml)	352	291	82.7%	61	348	2-33	12	7	18
2003-2004	6914	Rubella IgG positive (>10 IU/ml)	368	360	97.8%	8	341	0-150	20	12	29
2004-2005	7363	Rubella IgG positive (>10 IU/mL)	376	370	98.4%	6	375	2-55	16	11	27
2005-2006	7553	Rubella IgG positive (>10 IU/mL)	373	349	93.6%	24	373	0-162	17	9	27
2005-2006	7798	Rubella IgG positive (>10 IU/mL)	371	337	90.8%	34	395	4-38	13	9	21
2006-2007	8010	Rubella IgG positive (>10 IU/mL)	372	209	56.2%	163	402	0-500	10	5	16

NB. All specimens were derived from single donations with the exception of specimen 6359, which was from a pool of two donations.

Figure 2: Method medians for methods with ≥ 10 users



* N.B. Diamedix has 3-5 users, but was included in the graph due to its low method median

Figure 3: 5%-95% ranges of methods used to analyse specimen 8010

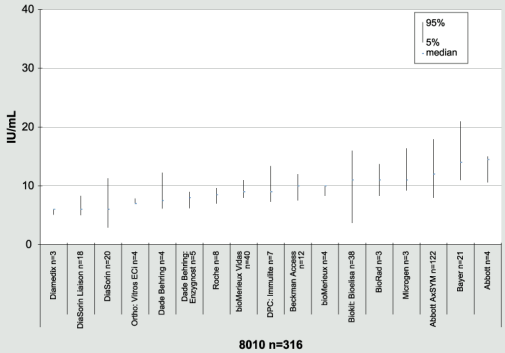
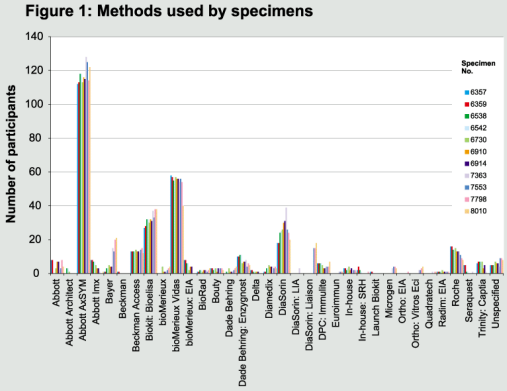


Figure 1: Methods used by specimens



Conclusions

Even though there has been an international standard for rubella available for many years there remains a difference in the quantitative results reported for different kits. For specimens containing low levels of antibodies this variation can result in the specimens being classified as coming from a patient who is non-immune.

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