

**An audit of rubella IgG antibody status in antenatal women in the Cwm Taf (south) NHS trust over a five
year period
(2005 – 2009)**

L. A. Matthews¹, L. M. Lawrance², D. Gray², S. Gray²

¹Address for Correspondence: Virology Laboratory, Pathology, Royal Glamorgan Hospital, South Wales CF72
8XR. linda.matthews@wales.nhs.uk

²Faculty of Health and Life Sciences, University of the West of England, Bristol, BS16 1QY.

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Summary

Rubella, a vaccine preventable infection, has serious implications for the foetus if contracted during pregnancy. This study examines the antibody status of 11987 pregnant women 2005 - 2009. Results show a non significant decrease in those with antibody levels of < 4.0 IU/ml from 29/2312 (1.3%) in 2005 to 21/2447 (0.9%) in 2009 (χ^2 for linear trend = 0.279; p=0.56) but a significant increase in those with levels <10 IU/ml from 88/2312 (3.8%) in 2005 to 124/2447 (5.1%) in 2009 (χ^2 for linear trend = 10.27; p=0.001).

In women born before 1983 (pre-pubertal vaccination) the proportion of first pregnancies with titres <4IU was 1.1% (21/2002) compared with 3.4% (69/2022) in those born after 1983 (χ^2 25.176 p<0.0001) and 2.2% (44/2002) for titres <10IU compared to 14.0% (282/2022) for those born after 1983 (χ^2 171.43 p<0.0001) .

The potential impact of the increase is difficult to determine, requiring further monitoring.

Introduction

Rubella is an infectious viral illness of childhood that can be so mild (or even asymptomatic) that most adults will be uncertain of their infection history. It can also be confused with other infections such as Parvovirus B19. Prior to immunisation programmes, rubella had a world-wide distribution occurring sporadically and epidemically in temperate climates, mostly in spring. Infection occurs most commonly among children and the resulting natural immunity is probably lifelong [1]. In pregnant women, the risk of intrauterine transmission is up to 90% if infection occurs in early pregnancy (8 - 10 weeks gestation), when the viraemia leads to placental infection and spread of the virus, which causes a chronic infection of the foetus leading to the development of Congenital Rubella Syndrome (CRS) [2], [3],[4],[5].

Early in 1960, three rubella vaccines were licensed, with a live attenuated vaccine based on the RA27/3 strain dominating. This strain is now included in the measles, mumps and rubella combined vaccine (MMR). In 1970, the USA adopted a policy of universal rubella vaccination for pre-school children [6]. In contrast, at the same time, Australia, the UK and parts of Europe initially adopted a selective programme aimed at pre-pubertal girls, female nurses and teachers who were deemed to be at risk of acquiring rubella, and may not have acquired it naturally before puberty. Later recommendations advised the screening of pregnant women for rubella immunity and the offer of immunisation post-partum if considered susceptible [7],[8]. In 1988, the UK introduced the MMR vaccination for all children aged 12 – 15 months, resulting in a fall in the number of cases of rubella. The incidence of CRS fell from an average of 48 births and 742 terminations between 1971 and 1975 to an average of 4 births and 9 terminations between 1991 and 1995 [8]. In 1994, to combat a predicted measles outbreak, all school children (ages 5 – 16 years) were offered a single dose of measles and rubella combined vaccine (MR) [8], which caused the rubella susceptibility rate amongst children aged 5 – 16 to fall to 3.7% [9]. Despite this, the incidence of rubella infection, confirmed by laboratory testing, rose in 1996. However, these cases were mainly males in the group 17 – 24 yrs that had not been included in the 1994 MR campaign. There was very little impact on the antenatal population, who in 1996 had a rubella susceptibility rate of 1.2% (parous) and 2% (nulliparous) [9]. Rubella vaccination

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of teenage girls was discontinued in 1996 and replaced by a second dose of MMR for pre-school children aged 4 – 5 [7].

Generally, the levels of reported rubella in the UK are low, with no confirmed cases of rubella in Wales since 2005 see HPA database [10], and fewer than ten cases in 2009 in the UK, see HPA database [11]. Similarly, incidence rates of CRS in the UK are low. Three cases of CRS were reported in the UK between 2005 and 2007 and none in 2008 [12]. Despite this, changes to vaccination strategies, and the variability of MMR uptake rates over the last ten years, make it important to get a picture of rubella status amongst pregnant women in the UK. In this study, we provide data on rubella antibody levels for 11987 women in one NHS Health Board area in South Wales between the years 2005 and 2009.

Method

Routine blood tests are undertaken for all pregnant women receiving ante-natal care; normally between 11 and 13 weeks of pregnancy. All blood screening request forms from pregnant women attending the Royal Glamorgan and Llwynypia hospitals were examined for the period 2005 to 2009 (three years retrospective and two year prospective collection) and age, gravida and stated immunization history was recorded. The immunization history was from personal or maternal recall and was not used in analysis as studies have shown that personal/maternal recall of immunization history is unreliable [13] [14]. Rubella testing was carried out using Diasorin ETI-RUBEK ELISA kit on an automated ELISA system, according to manufacturer's instructions. The calibrators for the assay are 0.0 IU/ml, 10 IU/ml, 25 IU/ml, 50 IU/ml and 200 IU/ml, and a graph is generated which gives accurate readings at the lower end down to zero IU/ml. The WHO now recommends a level of >10 IU/ml as a definition of immunity [15]. The cut-off used in this laboratory, in line with international guidelines, is 10 IU/ml i.e. <10 IU/ml is classed as susceptible, and ≥ 10 IU/ml is classed as immune [15], [16].

All tests with results <12 IU/ml were repeated using the Abbott AxSym automated analyser as per manufacturer's instructions (2005 – March 2009) and Biomerieux Vidas (April 2009 – December 2009). The

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laboratory takes part in the NEQAS quality assurance scheme and consistently has results above the mean for UK laboratories. All kits were CE marked, having been standardized to the WHO international rubella virus serum [16]. In cases where one result was ≥ 10 IU/ml and one <10 IU/ml; the lowest result was reported in clinical practice. Attempts to standardize rubella status reporting have recently been made, one 2007 study examined results of antibody testing carried out by reference labs in 21 countries [17]. Researchers defined a cut off of <4 IU/ml as seronegative, 4 -7 IU/ml as equivocal and > 7 IU/ml as seropositive. It was stated, however, that for women of childbearing age the defined cut off for immunity should be an antibody titre >10 IU/ml [17][18]. The Diasorin assay used in this laboratory was used by 4 of the 21 reference laboratories and gave 100% agreement on testing the negative samples but an underestimation of antibody in the positive samples [17]. A 2008 study of eight EIA kits included Diasorin, Abbott and Biomerieux kits and demonstrated that these kits had comparable sensitivity and specificity with no false positive results [16].

For the purposes of this study, therefore, we elected to use cut off of 10IU/ml to define immunity, and to avoid possible exaggeration of the results, only those sample where both tests were <10 IU/ml have been recorded as such. Where both test results are <4.0 IU/ml individuals are recorded as seronegative. Data was analysed by calculating the percentage of pregnant women screened in this area who presented with Rubella IgG antibody level of <10 IU/ml and <4.0 IU/ml for each year of the study (2005-2009), as well as for first and second (or subsequent) pregnancies. Trend analysis was conducted using the Statcalc component of Epi Info 6.0, and involved chi-squared calculations for linear trend to see if a significant trend existed for increasing Rubella antibodies across the five study years [19],[20] by all, first and second (or subsequent) pregnancies. In cases where no gravida was stated, data were included in the overall susceptibility calculations, but were omitted from first or subsequent pregnancy data.

A separate analysis was undertaken for those born before 1983, and those born between 1987 and 1992. Figures were also extracted for those having had the offer of differing immunization programmes; those born before 1983 would have been offered rubella vaccine pre-puberty, those born between 1987

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and 1992 would have been offered one dose MMR vaccine, an MR vaccine in 1994 and a second MMR in the catch-up programme of 2005, and those after 1992 would have had the standard MMR programme [7][8].

Results

Of 11,987 pregnancies screened, 4026 (33.6%) were first pregnancy and 7254(60.5%) second or subsequent pregnancy. In 706 cases (5.9%) no gravida was stated. The results are shown in Table 1. The results in Table 1 show a non statistically significant trend for a decrease in those with those with rubella antibody levels of < 4.0 IU/ml (defined as seronegative) for this period from 29/2312 (1.3%) in 2005 to 21/2447 (0.9%) in 2009 (χ^2 for linear trend = 0.279 ; $p=0.56$). In contrast there is a significant increase in those with rubella antibody levels <10 IU/ml for this period from 88/2312 (3.8%) in 2005 to 124/2447 (5.1%) in 2009 (χ^2 for linear trend = 10.27; $p=0.001$).

Analysis by cohort of women depending on their vaccination experience , looking at those born prior to 1983 who would have been offered rubella vaccine pre-puberty at a time when wild rubella virus was still in common circulation, and those born after 1983, who would have been offered the childhood vaccination programme or a catch up childhood immunization shows that the proportion of first pregnancies with titres <4IU was 1.1% (21/2002) compared with 3.4% (69/2022) in those born after 1983 (χ^2 25.176 $p<0.0001$) and 2.2% (44/2002) for titres <10IU compared to 14.0% (282/2022) for those born after 1983 (χ^2 171.43 $p<0.0001$) .

The cohort of mothers born between 1987 and 1992 would have been offered a range of immunization opportunities from a single MMR, to a school catch up and then the local catch up campaign for school children and young adults. The results of this cohort are shown in Table 2, and show a decline in the proportion of this group with rubella levels <4IU/ml and <10 IU/ml.

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No women born 1992 onwards were included in this study in 2005 or 2006; 6, 30 and 60 were identified in 2007, 2008 and 2009 respectively. Of these 96, almost a third (29/96) had rubella IgG antibody levels of <10 IU/ml and over ten percent (10/96) had rubella IgG antibody levels of <4 IU/ml.

Discussion

Overall, the results of this study show that there has been a significant increase in those with rubella antibody levels <10 IU/ml from 88/2312 (3.8%) in 2005 to 124/2447 (5.1%) in 2009 (χ^2 for linear trend = 10.27; $p=0.001$). The proportion with a level <4IU has not changed significantly over this time. However, this cohort includes both women who were born prior to 1983 and would have been offered pre-pubertal immunization with rubella, and those offered childhood immunization. The results in these two cohorts are very different; those born before 1983 have very low levels of seronegativity (<4IU/ml) and high levels of immunity (>10 IU/ml). This may reflect that fact that a high proportion of this group would have been infected with rubella in childhood, as the immunization programme at that time did not prevent the circulation of rubella in the community, and it is well recognized that natural immunity to rubella gives higher titres than vaccine induced immunity.

In those born after 1983, the prevalence of those with rubella antibody levels <4.0 IU/ml did not change significantly over time (detailed data not shown), from 2.2% in 2005 to 1.8% in 2009 (χ^2 for linear trend = 0.001 ; $p= 0.982$) and the rubella levels <10 IU/ml remained steady at 11% in 2005 and 9% in 2009 (χ^2 for linear trend = 1.43; $p=0.23$). The levels of seronegativity, which will reflect non-vaccination or low titres following immunisation, and of titres <10 IU/ml is higher than the pre-1983 cohort. There seem to be changing patterns within these cohorts, with the 1987-1992 cohort showing a decline in levels of antibody <4IU/ml and <10 IU/ml over the time period, but with very high levels of titres <10IU/ml in the (albeit small) post 1992 cohort. This may reflect the success of the 2005/6 catch up MMR campaign in Wales (see below).

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Rates of titres $<4\text{IU/ml}$ and for $<10\text{IU/ml}$ for second or subsequent pregnancies are lower than those for first pregnancy as would be expected with post partum immunization programmes. However, despite a policy of routine ante-natal testing and post-partum MMR vaccination, 7 (0.5%) of the women attending for their second pregnancy in 2009 had rubella IgG antibody levels of $<4\text{IU/ml}$ and 44 (2.9%) had rubella IgG antibody levels of $<10\text{IU/ml}$. Further work is underway to determine if this is due to system failure in vaccine delivery, or lack of response. However, In the last two quarters the antenatal services in this area failed to meet the 95% target for post partum immunization of women identified as having rubella IgG antibody level $<10\text{IU/ml}$ [21]. It is generally difficult to obtain accurate figures for uptake of post partum immunization rates as there is no requirement to notify adult MMR immunizations to a recording authority. One study showed that the uptake can vary between 5% and 80% [22] and in an English study carried out in the East of England and the West Midlands the uptake was 29% and 60% respectively [23].

The high number of women with rubella IgG antibody level $<10\text{IU/ml}$ in those born after 1983 are noteworthy. This level of response may reflect low levels of immunisation or lack of response to vaccination. In 1998, uptake of the MMR vaccine fell due to adverse publicity about its safety but is slowly increasing [24]. Uptake rates for MMR in Rhondda Cynon Taff, (of which the Health Board is the larger part), have increased from about 83% in 2003/4 to 90% in 2008/9 for first vaccination and 80% for second vaccination uptake, still well below the level required for herd immunity [24]. An MMR catch up programme was undertaken in Wales in 2005/6 but although immunization was received by 53,798 secondary school students and 7112 college or university students, over 73,000 identified as in need of at least one dose MMR did not accept immunization [25]. This cohort will shortly be reaching childbearing age.

The overall prevalence of antibody levels of $<10\text{IU/ml}$ is comparable to that recently reported from Sweden, where 95.5% of a cohort of 39,890 antenatal sera screened between 2004 and 2006 had levels $>10\text{IU/ml}$. The Swedish immunization programme differed from that in the UK in that the pre-pubertal rubella vaccine was replaced in 1982 by two doses of MMR at 18 months and 12 years [26]. Examination of

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primiparous women in this cohort demonstrated that of those born prior to 1980 who were routinely offered the monovalent rubella vaccine at 12 years of age and exposed to the wild virus still circulating in the community, 2.7% demonstrated levels of <10 IU/ml, compared to 8.7% of those offered two doses of MMR vaccine after 1982. This study also found higher levels of titres of <10IU/ml in those offered the childhood vaccination programmes. We are currently looking in more detail at the immunizations received by those individuals with low titres of rubella.

A key concern is whether an antibody titre of <10 IU/ml represents a risk of rubella acquisition should exposure occur. In their experimental study, O'Shea *et al.* demonstrated that 1/19 (5%) of those with a level <15 IU/ml (vaccine induced) and 8/10 (80%) of seronegative women (<1 IU/ml) could acquire infection if exposed [27]. They also found that if low level immunity was due to past infection it was unlikely that infection would occur. It must be stressed that this study was carried out using nasal challenge with the vaccine and may be of limited application in practice. As there has been no evidence of circulating rubella in the study area for many years it is unlikely that low level immunity (1 – 10 IU/ml) in those born after 1992 is due to past infection. Applying O'Shea's figures to data from this study would suggest that that in 2009, 13 women had levels of <4 IU/ml, and if considered seronegative, could potentially be infected during pregnancy in one year in the Trust area if the rubella virus was circulating. However the low prevalence of titres <4IU/ml make it unlikely a large outbreak would occur in South Wales.

While current figures show very low levels of circulating rubella in the UK, it is not only the risk of exposure within the UK that needs consideration. Many European countries have varied immunization programmes and coverage. For example, parts of Italy only have around 26% vaccine coverage and an elimination plan for rubella was only implemented in 2003 [28]. A 2004 Greek study found that 23.2% of women of childbearing age were susceptible to rubella [29]. Most Eastern European countries have introduced rubella/MMR vaccine in the last 5 – 10 years, but despite this Poland reported 20,000 cases of rubella in 2007 see Euvac database [30]. Finally, in South Africa, a country which has hosted several international sporting events in 2010, the measles vaccine is given as routine, but mumps and rubella are

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not part of the routine immunization schedule and rubella is not a legally notifiable disease, although 1072 cases were reported in 2007, see WHO database [31]. Low immunization rates and circulating rubella virus in countries such as Greece, Italy and South Africa pose a potential risk to pregnant holidaymakers, particularly given that investigations of cases of CRS showed that a high percentage of mothers had acquired infection abroad [7],[32]. For this reason, MMR vaccine is recommended by the HPA for travel to areas where prevalence is high and/or vaccine coverage is low, see HPA database [33]. In addition, there is a risk of importing rubella from these countries.

Although undertaken in one Trust area in South Wales, it is likely that these results can be generalised to other areas, as immunization schedules and the fall in uptake of MMR are UK issues. [34]. If anything, the data presented for this area may under-represent rubella susceptibility in other populations in the UK, as it is known this is higher in immigrant communities [8]. For example, Sri Lankan women living in Britain have rubella susceptibility rates between 15 and 23% [35],[36]. It was not possible to determine ethnicity for this study from the antenatal booking request forms but the 2001 census figures for the Rhondda Cynon Taff County Council area, of which the study area is a part, showed that 97.5% of the population were white British and 0.5% were white Irish, only 2% being in the "other" category, see ONS database [37]. Given this, it seems quite possible that levels of seronegativity and low antibody levels <4IU/ml and <10 IU/ml may be higher in areas where there is a higher percentage of mothers born overseas.

This study has demonstrated that there are changing patterns of rubella seronegativity and susceptibility in pregnant women born before and after 1983. The increase in the number of young women with levels of <10IU/ml requires further monitoring, particularly as the cohort experiencing low levels of MMR uptake in the late 1990s reaches child bearing age. Although to date the number of cases of CRS reported in the UK remain low and outbreaks of rubella are unlikely, these levels suggest there is potential for infection to be acquired or imported from abroad.

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Table 1: Antenatal blood screening results for rubella IgG at the Royal Glamorgan and Llwynypia hospitals: 2005 - 2009

	2005	2006	2007	2008	2009	χ^2 Analysis ²
Total pregnancies screened	2312	2312	2466	2450	2447	
Age range in years	14 - 44	14 - 45	14 - 46	14 - 46	14 - 45	
Median	27	27	27	27	27	
Rubella IgG <4.0 IU/ml	29 (1.25%)	26 (1.12%)	24 (0.97%)	38 (1.55%)	21 (0.86%)	$\chi^2 = 0.279$ p=0.56
Rubella IgG <10 IU/ml	88 (3.8%)	86 (3.7%)	97 (3.9%)	134 (5.5%)	124 (5.1%)	$\chi^2 = 10.37$; p=0.001
First pregnancies screened	760	777	824	844	821	
Rubella IgG <4.0 IU/ml	16 (2.1%)	20 (2.6%)	17 (2.1%)	26 (3.1%)	13 (1.6%)	$\chi^2 = 0.199$ p=0.656
Rubella IgG <10 IU/ml	50 (6.6%)	54 (6.9%)	64 (7.8%)	79 (9.4%)	78 (9.5%)	$\chi^2 = 9.985$; p=0.002
Second/subsequent pregnancies screened	1419	1383	1495	1448	1509	
Rubella IgG <4.0 IU/ml	9 (0.6%)	6 (0.4%)	7 (0.5%)	8 (0.6%)	7 (0.5%)	$\chi^2 = 0.168$ p=0.682
Rubella IgG <10 IU/ml	28 (2.0%)	28 (2.0%)	33 (2.2%)	54 (3.7%)	44 (2.9%)	$\chi^2 = 6.884$ p=0.007
Gravida not stated¹	133	152	147	158	117	

¹Figures not entered into the statistical trend analysis of the first and second pregnancy data.

²Statistically significant results reported in bold.

Table 2: Antenatal blood screening results for rubella IgG in those born 1987-1992 offered a single MMR plus catch-up immunization the Royal Glamorgan and Llwynypia hospitals: 2005 - 2009

	2005	2006	2007	2008	2009	χ^2 Analysis ²
Total pregnancies screened	143	227	345	455	506	
Age range	14-18	14-19	14-20	15-21	16-22	
Median	17	18	18	19	20	
Rubella IgG <4 IU/ml	9 (6.3%)	11 (4.8%)	4 (1.2%)	21 (4.6%)	12 (2.4%)	$\chi^2 = 3.008$ p=0.083
Rubella IgG <10 IU/ml	38 (26.6%)	43 (18.9%)	48 (13.9%)	86 (18.9%)	73 (14.4%)	$\chi^2 = 6.661$ p=0.009
First pregnancies screened	116	167	224	282	276	
Rubella IgG <4 IU/ml	6 (5.2%)	10 (6.0%)	4 (1.8%)	19 (6.7%)	8 (2.9%)	$\chi^2 = 0.450$ p=0.502
Rubella IgG <10 IU/ml	32 (27.6)	32 (19.2%)	40 (17.9%)	63 (22.3%)	53 (19.2%)	$\chi^2 = 0.817$ p=0.366
Second/subsequent pregnancies screened	19	51	108	141	255	
Rubella IgG <4 IU/ml	0	1 (2.0%)	0	2 (1.4%)	5 (2.0%)	$\chi^2 = 0.682$ p=0.41
Rubella IgG <10 IU/ml	3 (15.8%)	9 (17.7%)	8 (7.4%)	16 (11.3%)	20 (7.8%)	$\chi^2 = 5.480$ p=0.019
Gravida not stated¹	8	9	13	32	15	

¹Figures not entered into the statistical trend analysis of the first and second pregnancy data.

²Statistically significant results reported in bold.