Review of antenatal rubella susceptibility screening and the standard criteria for screening

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Literature review

Literature searches[1] were carried out in 2007, 2009 and October 2010, using broad search strategies to identify references relating to antenatal rubella screening, rubella infection, immunity, and immunisation, published between January 2003 and September 2010. Altogether 237 references deemed to be relevant were identified. A further 3 relevant references published October 2010-January 2011 were known to the reviewer.

Conference abstracts and unpublished local audits

A substantial number of local audits have also been conducted into the delivery of post-partum vaccination. Some of these have appeared as conference abstracts, others are unpublished.

National surveillance of congenital rubella is undertaken by the reviewer.

The reviewer scanned these references and other relevant sources.

The Condition

Rubella susceptibility in pregnancy, infection in pregnancy and congenital rubella infection

For this screening programme, identifying the condition is problematic. The primary condition of interest is rubella susceptibility, but the wider aim of the programme is to reduce or eliminate rubella infection in subsequent pregnancies thereby preventing congenital rubella infection and rubella-associated terminations.

The screening programme's stated aim is (a) to identify women who would benefit from rubella immunisation post-partum in order to protect the fetus in future pregnancies, should the woman come into contact with rubella infection, and (b) to ensure postpartum immunisation is offered.

Rubella susceptibility in pregnancy

At the time of the last review overall rubella susceptibility was estimated to be about 2.5% among antenatal women, on the basis of data collected 1996-1999, and it was recognised that in general, first generation immigrant women had higher susceptibility rates than women who were born in the UK and exposed to the schoolgirl or childhood vaccination programmes (Tookey et al, 2002). A more recent analysis of rubella susceptibility among new mothers, based on dried blood spot samples taken for newborn screening, was published in 2009 (Hardelid et al, 2009); this demonstrated four-fold higher susceptibility rates in women born in Sub-Saharan Africa, and five-fold higher rates in women born in South Asia, compared with UK-born women.

Recent data from the National Antenatal Infection Screening Monitoring (NAISM) programme show that the proportion of women categorised as rubella susceptible following confirmatory testing increased from 2.6% in 2005 to 3.9% in 2008 and 4.3% in 2009. (See

[1] Thanks to Nicola Pearce Smith and Paula Coles who performed the literature searches
August 2007 (Medline, Embase, Cochrane Library, National Library for Health) citations published May 2006-July 2007: 43 citations identified; September 2009 (Medline, Embase, Cochrane Library, NHS Evidence specialist collections) citations published Jan 2007-August 2009: 794 references, 53 deemed relevant (including 13 identified in 2007 search); October 2010 (Medline, Embase, Cochrane Library, PsychINFO, Cinahl, Web of Knowledge) citations published Jan 2003-Dec 2006, and Sept 2009-Sept 2010: 2257 references, 154 deemed relevant (no duplicates identified)

the later section on Programme Performance, for further discussion of the NAISM, test uptake and results).

Table 1 NAISM data on susceptibility to infection (IDPSP Annual Report 2008-2009, Table 4)
Proportion of pregnant women reported susceptible to rubella infection in England, 2005-2008

Region	2005			2006			2007			2008		
	Tests	Susceptible	% Susceptible	Tests	Susceptible	% Susceptible	Tests	Susceptible	% Susceptible	Tests	Susceptible	% Susceptible
East Midlands	21065	652	3.10	21995	533	2.42	25285	369	1.46	41348	1341	3.24
East of England	61862	1129	1.83	65269	1463	2.24	65723	1559	2.37	74212	2193	2.96
London	102931	4044	3.93	132008	5538	4.20	139331	5713	4.10	138243	6259	4.53
North East	27442	704	2.57	27735	979	3.53	33610	1180	3.51	33222	1771	5.33
North West	74768	1572	2.10	87580	1657	1.89	90237	1802	2.00	78688	2380	3.02
South East	71914	1562	2.17	85170	2278	2.67	106112	2829	2.67	99462	4099	4.12
South West	37848	766	2.02	45196	1091	2.41	50883	1364	2.68	50207	1653	3.29
West Midlands	72078	1435	1.99	69972	1788	2.56	69816	2044	2.93	76228	2603	3.41
Yorkshire & Humber	48394	1568	3.24	63318	1977	3.12	66823	2944	4.41	67646	3568	5.27
National	518302	13432	2.59	598243	17304	2.89	647820	19804	3.06	659256	25867	3.92

The reasons for the rise in susceptibility rates are unclear, but are likely to be related to variations in testing practices (see below 'The Test') and the demographic profile of the antenatal population.

Data from South Wales were recently published which explored the rubella status of 12,000 pregnant women between 2005 and 2009 (Matthews et al, 2010). For this analysis susceptibility rates based on antibody levels of <4IU/mL as well as <10IU/mL were explored. There was a non-significant decrease in the proportion of results <4IU/mL from 1.3% in 2005 to 0.9% in 2009, but a significant increase in results <10IU/mL from 3.8% in 2005 to 5.1% in 2009. At either level, women born after 1983 were much more likely to be susceptible than those born earlier. This dataset also included information on parity. At both levels women in their first pregnancy were 3-5 times more likely to be susceptible than women in their second or subsequent pregnancy, suggesting a possible relationship with previous post-partum vaccination.

Taking all this evidence into consideration, the proportion of pregnant women with rubella titres <10IU/mL is increasing, and there is no indication of any improvement in the susceptibility rates of first generation migrant women.

Rubella infection in pregnancy

Diagnosis of rubella infection in pregnancy is challenging , particularly as symptoms of rubella infection are often non-specific, or not present. Diagnosed rubella infection in pregnancy is monitored through routine notifications to the Health Protection Agency, and over the last decade there have been fewer than 5 notifications per year (www.hpa.org.uk). Medical reasons for pregnancy terminations are recorded for England and Wales by the Office for National Statistics; the annual number of terminations associated with rubella contact or infection in pregnancy has been fewer than 10 each year since 1999 (Abortion Statistics 2008, section 4.2.4).

Primary rubella infection in early pregnancy poses the highest risk of transmission to the fetus and fetal death or damage. A proportion of early maternal infections result in miscarriage and stillbirth. The likelihood of mother to child transmission and associated fetal damage is about 90% in the first few weeks of pregnancy, and gradually reduces to about 50% by the beginning of the second trimester. Although the risk of transmission then increases again towards the end of pregnancy, the likelihood of associated damage is remote after about 18 weeks (Miller et al, 1982). There is no evidence that any treatment is of benefit in the event of maternal rubella infection.

Women with confirmed rubella infection at any time in pregnancy need to be provided with clear information about the associated risks at different stages of gestation. Termination of pregnancy is an option, particularly if maternal infection occurred in the first trimester. Although serological testing can confirm maternal infection, pre-natal diagnosis and assessment of the likely outcome is not straightforward. Even if the fetus is shown to be infected, it is likely to be difficult to assess the extent of damage suffered, although anomaly scanning could identify gross defects of the heart and some other organs, and growth retardation.

Reinfection in pregnancy

Rubella reinfection is rare, but may become more common as population levels of rubella immunity decline, due to most immunity being conferred by vaccination rather than by infection with wild type virus. Rubella reinfection is usually asymptomatic, but symptomatic rubella reinfection is probably associated with higher levels of circulating virus. Limited evidence suggests that the risk of congenital rubella following symptomatic reinfection in early pregnancy is of the order of 8% (Bullens et al, 2000); this risk is tenfold lower than with primary infection, but nonetheless not negligible. Three congenitally infected infants have been reported to the NCRSP since 1996 whose mothers had confirmed reinfection in pregnancy (about 10% of all reports), and all 3 infants had CRS.

Congenital rubella infection

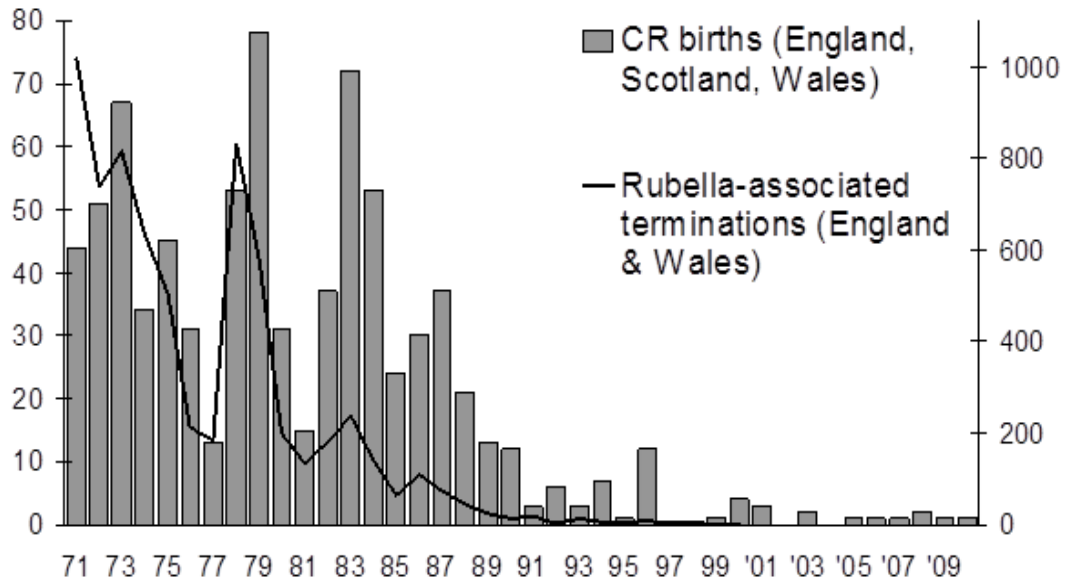
Before rubella vaccination was introduced in 1970 in the UK, about 18% of women of childbearing age were susceptible to rubella, and several hundred children were born each year with congenital rubella. Congenital rubella was estimated to be responsible for about 18% of sensorineural hearing loss, and 2% of congenital heart disease. Infants infected in the first trimester often have a constellation of rubella defects, usually involving the heart, eye and ear, and collectively described as congenital rubella syndrome (CRS) (South and Sever, 1985). Fetal infection occurring between about 10 and 16 weeks gestation is mainly associated with sensorineural hearing loss, usually without other defects. Survivors of congenital rubella infection have a greatly increased risk of developing autoimmune conditions (including thyroid problems and diabetes), often at a young age, as well as evolving hearing loss and ocular problems, and possibly psychiatric and behavioural disorders (Duszak 2009, Best 2007).

Current congenital rubella burden

The National Congenital Rubella Surveillance Programme was established in 1970 to monitor the impact of the newly introduced vaccination programme in England, Scotland and

Wales (Miller et al, 1997; Tookey and Peckham, 1999). As shown in Figure 1, there were substantial rubella epidemics in 1978/9 and 1983/4. The number of reported births did not substantially decline over the first 15 years of surveillance (average number reported was 50 a year 1971-75, and 40 a year 1981-85), although the number of rubella-associated terminations did (750 a year to 150 a year).

Figure 1: Congenital rubella births (NCRSP data) 1971-2010 and rubella-associated terminations (ONS data) 1971-2000*



*ONS have not reported number of rubella-associated TOPs since 2000 due to very small numbers

There have been very few confirmed reports of congenital rubella in recent years, and the last significant upturn in numbers was in 1996. Overall, and especially in recent years, a disproportionate number of infants with congenital rubella are born to women who were born abroad and were not able to take advantage of the UK's childhood immunisation programme. Since 2000 there have been 18 confirmed CR births in the UK, (NCRSP data, see BPSU Annual Report 2009-10; Tookey 2004). Almost all of the reported cases have substantial rubella-related damage, and it is likely that less obvious cases, for example, children with isolated sensorineural deafness, are under-reported. Nevertheless, the WHO goal of elimination has almost certainly been achieved in the UK, with less than 1 case reported in every 100,000 births since 1997.

The Test

Rubella susceptibility screening test

The purpose of the antenatal rubella susceptibility test, which is to identify women who would benefit from rubella immunisation post-partum, should be clearly explained at antenatal booking. It should be made clear that it is not a test for rubella infection in pregnancy. The current recommendation is that women should be advised at antenatal booking that if they develop, or are exposed to, a rash at any time in pregnancy, they should seek professional advice, regardless of whether or not they have had the screening test, or the result (IDPSP Standards Handbook 2010).

Current recommendations regarding the test itself are as follows (taken from IDPSP Laboratory Handbook 2010):

Screening Tests

- A sensitive immunoassay for rubella-specific IgG should be used, capable of providing quantitative results in IU/mL. Qualitative or semi-quantitative assays based on latex agglutination should not be used for the initial screening test.
- A result below 10 IU/mL is used to define rubella susceptibility.
- No report should be issued until a confirmatory test has been performed and a conclusion reached about the screening result.

Confirmation tests

- For screening test results below 10 IU/mL laboratories should repeat the analysis on the original specimen to confirm reproducibility and minimise the risk of laboratory error.
- Confirmation of an initial screening result of <10 IU/mL by an alternative analytical method is considered good laboratory practice.

Reporting results and standardised comments

- A report should be issued for every screening specimen received by the laboratory.
- For those specimens with antibody levels ≥10 IU/mL report 'Rubella antibody detected.'
- For those specimens with antibody levels <10 IU/mL report 'Rubella susceptible – 2 doses of MMR vaccination recommended post delivery.'
- For women who have already received two or more documented doses of rubella vaccine but still have levels of rubella antibody <10 IU/mL, further doses of vaccine are unlikely to be of benefit and protection against rubella can be assumed.

Test cut-off levels and low-level immunity

In earlier years the international cut-off for the rubella screening test was generally set at <=15IU/mL. The rationale for lowering the cut-off to <10IU/mL was outlined by Skendzel (1996):

The effectiveness of rubella vaccination is well documented and the 10 IU/mL antibody level is protective in the vast majority of persons. Sporadic reports of viremia and/or reinfection among previously immunized persons with low antibody levels have been reported but proven cases of reinfection have also occurred in persons with titers greater than or equal to the 15 IU/mL cut-off. Despite the occasional occurrence of rubella reinfection in persons with low titers, the theoretical risks are small especially as compared with significantly greater risk in persons who have not been vaccinated. Immunity in a given patient is a clinical decision and the results of antibody tests for rubella, like other laboratory tests, must be evaluated in the context of the clinical setting.

Although long term studies of rubella immunity in vaccinated individuals showed that protection appeared to be long-lasting (Christensen and Bottiger,1994; Davidkin et al, 2000) this was in the context of the continued circulation of wild virus, which could provide boosting to vaccine acquired infection. It is now evident that vaccine-induced immunity probably results in lower levels of rubella-specific antibody than naturally acquired infection (Mossong et al,2004; LeBaron et al, 2009). Although it is believed likely that low-level rubella immunity provides protection against wild type virus, the absolute limits of protection are unknown, and probably vary from person to person. A 2-dose policy similar to the UK programme has been followed in Finland since 1982. Davidkin et al (2000) reported on a fifteen year follow up of a cohort of children first immunised in 1982: one-third of those tested at age 17 had low level rubella antibodies, raising concerns about long-term protection. It is unclear whether additional vaccine doses in adolescence, or indeed for women postnatally, would result in prolonged maintenance of higher (and possibly more protective)

antibody levels. Investigation of the protective immunity conferred by low levels of antibody may be required.

Laboratory survey 2009

As part of the recent review of antenatal infection screening (concentrating on HIV, Hepatitis B and syphilis) a national laboratory survey was carried out in 2009 to clarify laboratory practices;[2] about two thirds of laboratories provided responses. Among the 82 laboratories which provided information on the cut-off value they used for the initial rubella susceptibility test, 4% used a value <8IU/mL, and about 15% used a value of 12IU/mL or greater. For the confirmatory tests, of the approximately 60 laboratories providing data, 5% used a cut-off <=5IU/mL, and 8% a cut-off =>15IU/mL.

Rubella infection and reinfection

Antenatal screening for rubella susceptibility plays no part in the diagnosis of recent or current infection. The screening test cannot distinguish between long-standing rubella immunity and recently acquired infection or reinfection. A rubella immune result at screening does not exclude prior infection in pregnancy. By the time women are tested and receive their rubella result, they are likely to have passed through the 1st trimester of pregnancy when rubella would be most devastating; those who are identified as rubella susceptible at screening will normally therefore be at low risk of having an infant with congenital rubella if they subsequently become infected. Women who present with rash illness or contact at any time in pregnancy, prior to rubella screening or after, and regardless of their screening result, should be managed in accordance with the published guidelines from the HPA which provide a diagnostic algorithm (Guidance on Viral Rash in Pregnancy, HPA 2011). Although rubella is unlikely to cause any problem after 18 weeks, a rash could indicate other conditions which should be investigated.

The Treatment

Management of women identified on screening as rubella susceptible

Women identified as rubella susceptible on screening require post-partum vaccination with a rubella-containing vaccine, and the current policy is that they should receive two doses of MMR. Those who report previous vaccination or have been told they are rubella immune in a previous pregnancy might require further explanation about the screening test and the likelihood that low-level antibodies are protective, although postpartum vaccination should still be advised unless there are at least two documented previous doses of MMR (or rubella vaccine).

In the past, when single rubella vaccine was available, only one post-partum vaccination was mandated following a rubella-susceptible screening result. A single dose of rubella containing vaccine confers 95-100% protection for rubella (Plotkin 2004). No single dose rubella vaccine is now licensed in UK, and the two rubella containing vaccines currently in use are Priorix© (GlaxoSmithKline) and MMRVaxPRO© (Sanofi Pasteur MSD). Both are triple MMR vaccines containing live attenuated virus strains including the Wistar RA27/3 strain of rubella virus (DH Green Book 2006).

Programme Performance

The HPA National Antenatal Infection Screening Monitoring (NAISM) programme was set up in 2004 to monitor the uptake and test results of antenatal screening for syphilis, hepatitis B, HIV and rubella susceptibility at regional and national level. Information is collected at maternity unit or trust level and supplied to HPA Regional Epidemiologists and NSC Regional Antenatal and Child Health Screening Managers. Regional data have been

[2] Thanks to John Marshall and David Worthington for access to the unpublished data

published for London (Giraudon et al, 2009), and Annual Reports are prepared and available at www.hpa.org.uk.
Interpretation of the data collected can be problematic as, for example, different trusts use different methods for ascertaining denominator data to estimate test uptake, and in some areas it has been difficult to distinguish antenatal samples from others or to exclude duplicate samples. Nevertheless, the data suggest that overall uptake of antenatal rubella screening is high, exceeding 95% overall in 2008 and 2009 (IDPSP 2008-2009 Annual Report).
There is currently no national monitoring of the delivery of post-partum vaccination of women identified as rubella susceptible and requiring vaccination.
Post-partum vaccine delivery: local audits
Local audits have been carried out in a number of English trusts and regions to explore the recording of the requirement for post-partum vaccination, and the delivery of vaccination to identified women. Few have been published, but a number have been presented at conferences, or were made available for this review.[3]
It was not possible to compare audit findings across regions or over time. Some audits covered a period as short as a month or three months, others reviewed data collected over a number of years. The data collected and the categories used were diverse and not standardised. Most audits were carried out in individual trusts, and included between 50 and 200 reports of women with a rubella susceptible screening result. In some cases it was reported that a substantial proportion of notes were unavailable. No audit reported on the delivery of two doses of vaccine. The proportion of women who received at least one dose of vaccine varied from approximately 20% to 80%, but who was included in the denominator was often unclear.
A similar variation in policy and practice was been documented in a Welsh review in 2007. Data were provided by 9/13 trusts, and 56% of susceptible women were recorded as having received one MMR, with considerable variation between trusts.

Summary
In summary, despite the slow improvement in MMR coverage, the situation with regard to rubella susceptibility and the potential for outbreaks of rubella to occur, putting susceptible pregnant women at risk, has not changed substantially since 2003.
Uptake of the rubella susceptibility screening test is consistently high, and the overall proportion of women with a susceptible result on screening in England increased from about 2.6% in 2005 to almost 4% in 2008. Currently the available audits on post-partum vaccine delivery vary in their methodology, but suggest substantial variation between trusts and regions. In the absence of standard monitoring of post-partum vaccine delivery rates, and up-to-date data on rubella susceptibility by parity, it is difficult to assess the practical impact of the programme adequately. However, it is likely that the vast majority of rubella-susceptible women are identified through the antenatal screening programme, and overall about half of them probably receive at least one post-partum MMR. Since the rubella component of the vaccine is highly effective, this is likely to provide protection in any future pregnancy to virtually all vaccinated women.

Conclusion

- This review found no evidence to change the main conclusion of the previous UK NSC review, that antenatal screening for rubella susceptibility does not meet the UK NSC criteria for the introduction of a screening programme.

[3] Thanks to the Regional Screening coordinators and colleagues who conducted these audits

- The current antenatal screening policy was introduced in the 1970s as an adjunct to the selective schoolgirl immunisation programme in the context of the circulation of significant levels of wild type virus in the general population. The mass immunisation policy changed the epidemiology of rubella in the UK, the context in which screening takes place and the contribution made by postnatal vaccination to the primary prevention programme. Lack of systematic monitoring makes the current contribution of screening and post-partum vaccination difficult to assess.
- The previous policy review (reported in 2003) concluded that, in the context of the mass immunisation programme, antenatal screening for rubella susceptibility did not meet the criteria for a screening programme. However, given the context of sub-optimal MMR uptake, it was considered an inappropriate time to reverse the policy.
- The UK incidence of congenital rubella syndrome is below the WHO criteria of elimination (less than 1 case of congenital rubella per 100,000 live births). However, as susceptibility rates appear to be increasing, and a substantial cohort of unimmunised children and young adults exists, there continues to be a risk that rubella could reappear in the UK.
- While the current policy presents an opportunity for some susceptible women to be vaccinated , antenatal screening and post-partum vaccination do not substantially impact on the continuing risk of rubella outbreaks occurring in the UK.
- As a public health problem, rubella susceptibility is most effectively addressed prior to pregnancy through the MMR immunisation programme. Antenatal screening does not prevent or reduce the risk of congenital rubella syndrome in the current pregnancy (and many women have only one pregnancy). A focus on the management of rash illness and exposure to rashes in pregnancy may be a more appropriate use of midwifery time. The current test may also falsely reassure women with a recent rubella infection.
- This review has highlighted a number of practical issues relating to the screening standards. These include standardisation of the test cut off values and systematic implementation of the postnatal immunisation programme. Addressing these would require an implementation drive which might be disproportionate in terms of the benefit to current pregnancies and the contribution to the wider primary prevention programme.

Recommendation

Policy makers should revisit i) the future of antenatal screening for rubella susceptibility and ii) primary prevention initiatives which might be directed towards population groups which continue to be at risk of rubella infection, including children, young adults and immigrants.

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