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Rubella in the United Kingdom

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HISTORY

The first description of rubella in the UK was by an English physician, Dr William Maton, who reported an outbreak of an illness resembling a mild form of scarlatina in a boys' public school in 1815 [1]. Some years later, when observing the spread of a rash-associated illness in a large family, Maton described the characteristic clinical features of rubella, namely a mild prodromal illness followed by a generalized and often tingling rash lasting for a few days and associated with enlarged and tender glands in the occipital and postauricular regions. He also correctly identified the relatively long incubation period of rubella and noted the absence of fever and other signs of constitutional upset. Maton did not suggest an English name for this disease which had been previously described and called Rothëln by German physicians in the late 18th century. The term 'rubella' (Latin for 'little red') was first used in 1866 by another English physician, Dr Henry Veale, when describing an outbreak of Rothëln in a boys' school in India [2].

Because of the mild nature of the disease, rubella received little attention for the next 100 years until the historic observation by Gregg of an association between maternal rubella and congenital cataracts [3]. The occurrence of a rubella epidemic in Australia in 1940 provided Gregg with the opportunity to observe the association and, although there is no doubt that he was a remarkably astute clinician, it is perhaps suprising that the connection was not made earlier. A massive epidemic of rubella in the United States in 1964/5 left an estimated 20000 rubella-damaged children in its wake and it seems unlikely that the problem of congenital rubella would have remained unnoticed if similar epidemics affecting a substantial proportion of the adult population had occurred in Europe or the US in the early part of the 20th century. This suggests that the average age of infection in these countries may have increased during this century possibly as a result of demographic or sociological changes in the population.

There is little information on the epidemiology of acquired rubella or the incidence of congenital rubella syndrome (CRS) in the UK before the introduction of selective vaccination in 1970. Information on the epidemiology of acquired rubella since 1967 is available from clinical reports to the Royal College of General Practitioners from 'sentinel practices', and from reports to the Communicable Disease Surveillance Centre (CDSC) from laboratories in England and Wales. Surveillance of congenital rubella was established in 1971 with the formation of the National Congenital Rubella Surveillance Programme (NCRSP) – a passive reporting system for infants with confirmed or suspected congenital infection. Other sources of epidemiological data include serological surveys of age-specific

rubella antibody prevalence and figures provided by the Office of Population Censuses and Surveys (OPCS) on the annual number of rubella-associated terminations of pregnancy. Rubella was only made a nationally notifiable disease in October 1988, when the UK selective rubella vaccination programme was augmented by the introduction of combined measles/mumps/rubella (MMR) vaccine for children.

This paper uses the above sources of data to review the epidemiology of acquired and congenital rubella in the UK before and after the introduction of rubella vaccination. The results of prospective studies carried out in the UK which have helped to define the magnitude and nature of the risk to the fetus of maternal rubella at successive stages of pregnancy are also reviewed.

EPIDEMIOLOGY OF ACQUIRED RUBELLA

Both RCGP and laboratory reports show that rubella follows a 3–5 year epidemic cycle with annual increases in spring and early summer – seasonal features which have remained unchanged since 1967 (Fig. 1). Before the introduction of vaccination, the age distribution of clinically diagnosed cases showed that rubella was predominantly a disease of school children, with 50% of cases occurring in the 5- to 14-year age-group (Table 1). The higher incidence of clinically diagnosed rubella in females than males, probably reflects greater concern about the disease in adult women and therefore greater readiness to seek medical advice. Clearly, the incidence rates in all groups in the Table are an underestimate of the true infection rates as rubella is usually a mild, and in some cases asymptomatic infection, so medical advice is often not sought.

Although clinical diagnoses of rubella may be unreliable, the age-distribution of RCGP reports is nevertheless consistent with serological findings which show an average age of infection for rubella of about 10–11 years [4]. This data was obtained in 1986/7 as part of a national survey carried out to establish the age/sex specific antibody prevalences to measles, mumps and rubella before the introduction of MMR vaccination [5]. Because of the effect of selective vaccination on rubella susceptibility in females, only the serological results for males could be used to estimate the epidemiological parameters of acquired rubella before the introduction of mass vaccination [4].

The decision to augment the selective vaccination programme by mass vaccination was based on the results of serological surveys of antenatal populations carried out during 1985–8 [6–8]. These indicated that despite high vaccine uptake, 2–3% of adult women were likely to remain susceptible and that to eliminate CRS it was necessary to interrupt circulation of wild rubella virus. MMR vaccine was therefore introduced in October 1988 for children aged 1–2 years in place of measles vaccine, and for children aged 4–5 years when they present for pre-school booster doses of diphtheria/tetanus vaccine. The latter component was designed as a 'catch-up' programme for the initial 3 years until the first cohorts of 1- to 2-year-old children offered MMR vaccine reached school age. There was an enthusiastic response to the new vaccination programme and by February 1991 coverage for 2-year-olds had reached 89%, which is 9% higher than the former coverage for measles vaccine [10]. Although uptake rates for

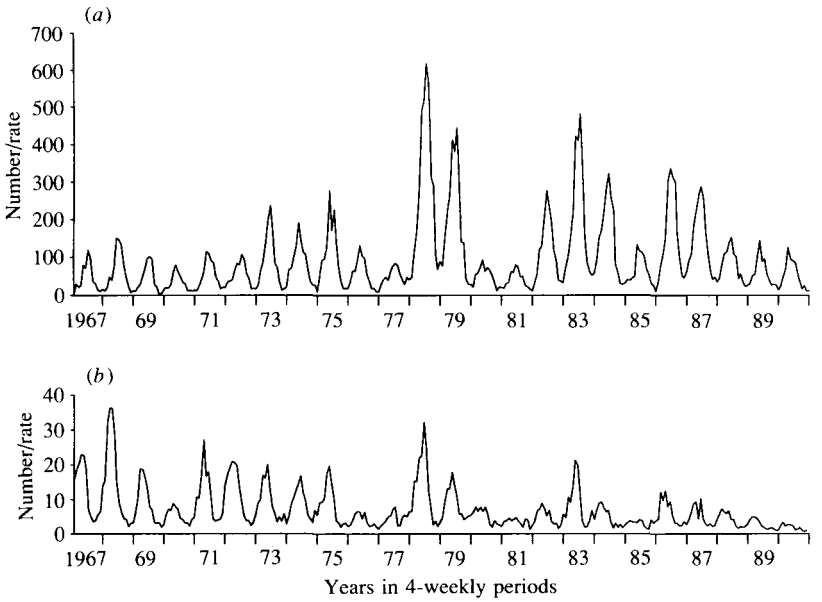

Fig. 1. Rubella virus reports (*a*) and RCGP consultation notes (*b*), for England and Wales, 1967–90.

Table 1. *Age group and sex of clinical cases of rubella reported to the RCGP during 1967–9*

	No. of cases	% of total	Average annual incidence rate per 1000
Total cases	2986	100	6·6
Age group (years)			
0–4	845	28	23·3
5–14	1502	50	22·7
15–44	587	20	3·2
⩾ 45	33	1	0·2
Not known	19	1	8·8
Sex			
Male	1320	44	6·1
Female	1666	56	7·1

preschool children are not yet available, sales figures indicate that MMR vaccine has been used extensively both in this age group and in older children [9].

The widespread use of MMR vaccine in children of all ages has already had a marked effect on the incidence of acquired rubella in the population. Rubella notifications to OPCS show a downward trend over the last 2·5 years with an annual total of 24570 cases reported during 1989 compared with 11482 during 1990; measles notifications show a similar reduction over the period reflecting the recent increase in measles immunization with the combined MMR vaccine. The cyclical pattern in the number of laboratory and RCGP rubella reports since 1967 (Fig. 1) suggests that, without the introduction of MMR vaccine, an epidemic would have occurred in 1990. Within 2 years therefore, mass rubella vaccination

has interrupted the epidemic cycle of the disease in the UK and reduced its incidence to a low endemic level.

INCIDENCE OF CONGENITAL RUBELLA

Although there are no figures for the annual number of rubella-handicapped children born before 1971, some idea of the incidence of CRS in the pre-vaccine era can be obtained by estimating the proportion of children in the population with sensorineural deafness attributable to rubella. In a survey by Peckham and her colleagues of 568 children aged under 4 years attending the Nuffield Hearing and Speech Centre between 1972 and 1975, rubella antibody was found in 24% of the 349 with sensorineural deafness compared with only 9% of the 219 children with other problems [11]. This implies that about 15% of the 2·5/1000 children born with sensorineural deafness are damaged as a result of congenital rubella. Similarly it was estimated that about 2% of the 6/1000 children born with a congenital heart defect have rubella embryopathy [11]. Since the majority of rubella-attributable heart defects occur in association with deafness, it was estimated that, in a non-epidemic year, about 200–300 of the 650000 children born in England and Wales have congenital rubella defects [11]; the number of rubella-damaged children born in an epidemic year could be up to 10 times as many.

The introduction of selective rubella vaccination had no immediate effect on the incidence of CRS although there has been a significant downward trend in the annual number of reported cases over the last 20 years [9]. Births of children with CRS, however, are only one of the adverse consequences of rubella in pregnancy and, to assess fully the impact of the UK vaccination programme, the annual number of rubella-associated terminations of pregnancy must also be considered (Fig. 2); these display a downward trend similar to that seen in the number of reported CRS cases. Both indices clearly show the disastrous effects of rubella epidemics. In the epidemic year of 1978, for example, there were 56 children reported to the NCRSP and 830 terminations of pregnancy for rubella, compared with 17 and 184 respectively in the non-epidemic year of 1977 [9].

SURVEILLANCE OF RUBELLA SUSCEPTIBILITY AND INFECTION IN PREGNANCY

Surveillance of rubella antibody prevalence according to age and parity has played a major role in assessing the effect of selective vaccination and has allowed the separate contributions of schoolgirl vaccination, and of pre-pregnancy and post-partum vaccination of susceptible adult women, to be identified [6]. Serological results for the Manchester antenatal population (about 40000 women annually) since July 1984 are shown in Fig. 3. The difference in susceptibility between nulliparous and parous women is apparent in all age groups and therefore reflects the effect of post-partum vaccination. Both parity groups show a significant downward trend in susceptibility since 1984 ($P = < 0{\cdot}0001$, Poisson distribution with correction for overdispersion), evidence of the increasing effectiveness of all components of the selective vaccination programme over the last 6·5 years. Overall, of the 36613 pregnant women tested in 1990, only 406

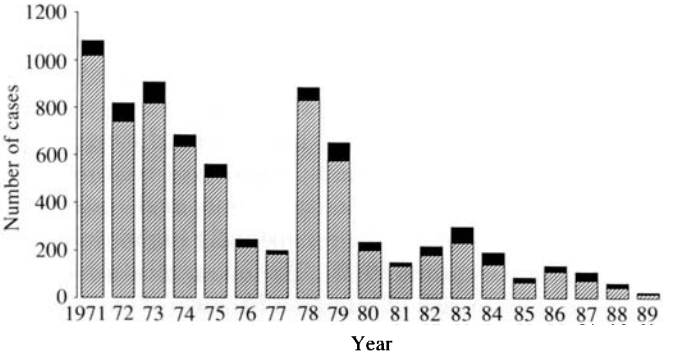

Fig. 2. Congenital rubella cases (■) and terminations of pregnancy for rubella (▨) (disease and contact), England and Wales, 1971–89.

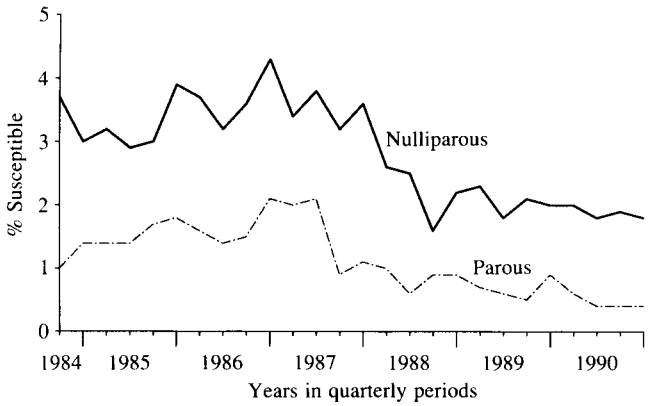

Fig. 3. Rubella susceptibility in the Manchester antenatal population (July 1984 to December 1990).

Table 2. *Risk of laboratory-confirmed rubella infection in susceptible pregnant women in the Manchester antenatal population 1983–90*

Year	Number susceptible	Number infected	Infection risk/ 1000 susceptibles
1983	1519	30	19·7
1984	1107	27	24·4
1985	927	4	4·3
1986	1073	10	9·3
1987	1013	17	16·8
1988	601	8	13·3
1989	468	3	6·4
1990	406	1	2·5

(1·1%) were susceptible compared with 249 of 2463 (10·1%) age-matched males from the Manchester area who were tested between 1984–7.

The annual number of laboratory-confirmed cases of rubella infection in women in the Manchester antenatal population has also been recorded since 1983, and provides a minimum estimate of the risk of rubella infection in suseptible pregnant women in the area (Table 2). Annual infection risks show the cyclical pattern of local rubella epidemics, with 2 years of high incidence followed by 2 years of low

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incidence. The number of maternal infections which are not serologically diagnosed is unknown although figures from the NCRSP confirm that the laboratory ascertainment of infections during the early months of pregnancy is not complete. Of the 118 mothers of infants with congenital rubella born between July 1978 and June 1980, 49 (42%) had no laboratory investigations during pregnancy even though 25 had a rash and a further two had a history of contact [12].

Before the introduction of MMR vaccine, confirmed infections rates in susceptible parous women were found to be consistently higher (about 2- to 3-fold) than in susceptible nulliparous women [6, 9]. The interpretation of this finding is that parous women are at greater risk of infection because of exposure to their own children with rubella. In 1989 this trend was reversed and, for the first time, infection rates were lower in susceptible parous than nulliparous women [9]. Overall, only 52 laboratory-confirmed infections in pregnancy were reported to CDSC during 1989 and 20 during 1990, the lowest annual totals since surveillance began. Such figures contrast sharply with the total of 1376 infections reported during the epidemic year of 1978.

These observations confirm that the MMR vaccination programme has already had a substantial effect on the epidemiology of acquired rubella, and has significantly reduced the risk of exposure of pregnant women to children with rubella. A further reduction in the number of children reported to the NCRSP and in the number of rubella-associated terminations of pregnancy should therefore be apparent in the future.

STUDIES OF THE OUTCOME OF RUBELLA INFECTION IN PREGNANCY

Following the publication of Gregg's paper in 1941 [3], large-scale investigations were carried out in Australia to confirm and extend his original observations. Although no prospective studies were undertaken, the Australian workers nevertheless concluded that 'on the available evidence, when a women contracts rubella within the first two months of pregnancy it would appear that the chances of her giving birth to a congenitally defective child are in the region of 100%' [13]. This assessment was rightly criticized as it was based on retrospective studies in which the mothers of infants with congenital defects were asked about the occurrence of rubella during pregnancy. The results of small prospective studies carried out in the USA, Sweden and England during the 1940s suggested that the risk to the fetus of early gestational maternal rubella was substantially lower than that claimed by the Australian workers.

Outcome of clinically-diagnosed rubella infection in pregnancy

The importance of undertaking large prospective studies, and of comparing the outcome of pregnancy in infected women with that in a control group, was recognized in the UK and in 1950 a national study was set up by the Ministry of Health [14]. Although the study was principally designed to assess the risk of fetal damage following maternal rubella, the outcomes of pregnancies in which mothers had measles, mumps, chickenpox or poliomyelitis were also studied. Doctors and midwives in England, Scotland and Wales were asked to question pregnant women and illnesses that had occurred before the first or between subsequent

antenatal visits. Women reporting any of the five virus infections were identified and clinical confirmation of the diagnosis sought from the patient's family doctor. A 2% sample of control women was selected by recruiting antenatal patients without a history of virus infection and with birthdays on the 31st day of any month. Virus-infected and control women were followed up to determine the outcome of pregnancy and brief annual medical reports obtained for liveborn infants up to 2 years of age.

Between July 1950 and December 1952, a total of 5717 control and 1513 virus-infected women were followed up; 578 of the latter had clinically diagnosed rubella. There was a significantly higher incidence of spontaneous abortions and still births among the rubella-infected than the control pregnancies, the differences being most marked during the first trimester. Of the live born infants, 15·8% of the 202 whose mothers had rubella before the 13th week of pregnancy had a major congenital defect reported by 2 yeras of age; the risk after the 13th week (2·2%) was similar to that in the control group (2·3%). A full audiometric and developmental assessment was subsequently carried out at 3–5 years of age in 57 children whose mothers had rubella during the first 4 months of pregnancy. These detailed examinations identified a further 14 children with sensorineural deafness as their only defect, raising the estimated risk of damage following maternal rubella during the first 16 weeks of pregnancy to 33%. They also demonstrated the value of repeated audiometric assessment in children exposed to early gestational maternal rubella.

Despite the regorous epidemiological methods used in this first UK study, it did not provide a definitive answer to the researchers' question 'What is the risk of a defective baby following an attack of rubella in pregnancy?' [14] as it lacked one essential element – the laboratory confirmation of maternal rubella infections. It was not until the isolation of rubella virus in 1962 and the subsequent development of diagnostic tests that the unreliability of a clinical diagnosis became evident. The occurrence of asymptomatic primary infection, and of rubella reinfection in individuals with serological evidence of prior infection or successful vaccination, was also demonstrated. An earlier report by the Australian workers of four cases of typical CRS without a maternal history of rubella [13] suggested that asymptomatic infection could present a risk to the fetus. There was therefore a need for further prospective studies to assess the risk of fetal damage following laboratory-confirmed matenal rubella, and the risk following primary asymptomatic and rubella reinfection in pregnancy.

The development of virus isolation and serological techniques for the diagnosis of congenital rubella allowed the fetal infection rates, and the risk of defects in infected infants, following maternal rubella at different stages of pregnancy to be investigated. The first UK study to assess the risk of defects in children with confirmed congenital infection was carried out by Peckham [15]. She examined 218 children whose mothers developed clinical rubella during 1960–2 despite post-exposure immunoglobulin prophylaxis. Although serological techniques for diagnosing rubella were not available at the time of the mothers' infections, congenital infection could be diagnosed in 118 (55%) of the 218 children by the detection of persistent rubella antibody at 1–4 years of age. Of the 98 infants infected during the first 16 weeks, 33 (34%) had rubella defects. Reassessment of

84 children at 6–8 years of age revealed additional hearing defects in seropositive children but none in those who were seronegative at 2 years of age. Inclusion of these cases raised the estimated risk of defects in infants infected during the first 16 weeks of pregnancy to 71%. Peckham's study confirmed that some children develop late onset deafness and showed the value of serological testing to identify those who are at risk.

Outcome of confirmed symptomatic rubella infection in pregnancy

The first opportunity to carry out a large prospective study to assess fetal infection rates and the risk of defects following confirmed symptomatic matenal rubella at successive stages of pregnancy came during the 1978/79 epidemic. Sera from 258 infants whose mothers had a rash diagnosed as rubella by a Public Health Laboratory Service (PHLS) laboratory in England and Wales were examined at Manchester PHL [16]. Evidence of congenital infection was found in 117 (45%) by the detection of rubella-specific IgM antibody by capture radioimmunoassay (MACRIA) soon after birth and/or the persistence of IgG antibody after the first year. The frequency of congenital infection was highest during the first trimester (> 80%), declined to a minimum at 23–26 weeks and then rose again to high figure near term. Serological testing at Manchester PHL of a further 162 infants whose mothers had laboratory-diagnosed symptomatic rubella during 1983–7 has confirmed these findings. The results for the two study periods are shown in Table 3.

To date, 141 of the 190 congenitally infected children in the PHLS study have been followed to 2 years of age; rubella defects were found in 37 (26%), all of whom were infected before the 19th week of pregnancy (17). Of the 20 children infected during the first 10 weeks, 18 (90%) had sensorineural deafness; 8 of these children also had congenital heart disease. Fifty per cent of those infected between 11 and 12 weeks and 33% of those infected between 13 and 16 weeks had sensorineural deafness but no other defects at follow up. The factors which determine whether an infant infected between 11 and 16 weeks will subsequently develop deafness are unclear but the risk does no appear to be greater for those who suffer the intrauterine growth retardation effects of congenital rubella [16]. After 16 weeks the risk of deafness declines sharply [18]; follow-up of 15 of the 21 infants infected between 17–18 weeks detected mild sensorineural deafness in only one child [17]. Various other abnormalities such as orthopaedic problems and mild developmental delay have been reported in children exposed to maternal rubella after the 18th week of pregnancy, but with similar incidence in seronegative and seropositive children [16].

The overall risk of having a rubella-damaged child following confirmed symptomatic infection during the first 18 weeks of pregnancy is obtained by multiplying the fetal infection rate at each stage by the risk of defects if infected. Using the results of the PHLS study, this gives an estimated risk of 90% between 2 and 10 weeks, 34% between 11 and 12 weeks, 17% between 13 and 16 weeks and 3% between 17 and 18 weeks. The original claim that nearly 100% of fetuses are damaged following maternal rubella during the first 2 months of pregnancy made by the Australian workers on the basis of retrospective surveys has therefore been confirmed by prospective surveys confined to laboratory-proven cases. Despite the improved epidemiological methods of the prospective studies carried out in the

Table 3. *Outcome of serologically-confirmed symptomatic maternal rubella cases reported to the PHLS communicable Disease Surveillance Centre*

Stage of pregnancy	Study period								
	1976–8			1983–7			Total		
Completed weeks between rash and LMP	Infants tested	Infected* No.	(%)	Infants tested	Infected† No.	(%)	Infants tested	Infected No.	(%)
2–< 11	9	9	(100)	11	11	(100)	20	20	(100)
11–12	6	4	(67)	16	12	(75)	22	16	(73)
13–14	18	12	(67)	12	7	(58)	30	19	(63)
15–16	36	17	(47)	17	7	(41)	53	24	(45)
17–18	33	13	(39)	23	8	(35)	56	21	(38)
19–22	59	20	(34)	23	6	(26)	82	76	(32)
23–26	32	8	(25)	25	6	(24)	57	14	(25)
27–30	31	11	(35)	21	9	(43)	52	20	(38)
31–36	25	15	(60)	11	6	(55)	36	21	(58)
⩾ 37	8	8	(100)	3	1	(33)	11	9	(82)
Total	257	117	(45)	162	73	(43)	419	190	(45)

* IgM antibody detected by IF or MACRIA using a labelled polyclonal antibody and/or persistent IgG antibody detected by IF.

† IgM antibody detected by MACRIA using labelled monoclonal antibody (persistent IgG not tested).

UK and elsewhere during the 1950s and early 1960s, they nevertheless provided a less accurate estimate of fetal risk than the Australian studies because, without laboratory confirmation of maternal infections, inclusion of non-rubella cases was inevitable.

Outcome of periconceptional symptomatic maternal rubella

Although there have been isolated reports of possible congenital infection following maternal rubella before pregnancy, in none of these cases was the diagnosis in the mother or the fetus confirmed by adequate laboratory techniques. The only published study of the outcome of confirmed periconceptional maternal rubella was conducted jointly in the UK and West Germany and reported the fetal infection rate in 61 pregnancies in which onset of maternal rash was between 5 weeks before to 6 weeks after the last menstrual period (LMP) [19]. No evidence of infection was found in the products of conception or the children resulting from 38 pregnancies in which the mothers' rash appeared before or up to 11 days after LMP. The earliest time at which fetal infection occurred was when onset of maternal rash was 12 days after LMP. Thereafter, the proportion of fetuses infected increased sharply, reaching 100% by 21 days. Although the number of cases in the study was relatively small, the findings nevertheless suggest that the risk to the fetus starts at about the time of conception.

Outcome of primary asymptomatic and rubella reinfection in pregnancy

The first study of the outcome of asymptomatic rubella infection in pregnancy was carried out in the UK by Peckham [20]. She identified 60 children whose mothers had confirmed rubella despite post-exposure immunoglobulin prophy-

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laxis; 34 women had a rash and 26 were asymptomatic. Maternal infection was diagnosed by demonstrating seroconversion using neutralization or haemagglutination inhibition (HI) methods. At follow-up, only 5 (19%) of the children whose mothers were asymptomatic had persistent rubella antibody compared with 18 (53%) of those whose mothers had a rash; the corresponding numbers of children with congenital rubella defects were 1 and 9 respectively.

Although Peckham's study suggested that asymptomatic maternal rubella may present less risk to the fetus than clinical rubella, the serological techniques used to diagnose maternal infection were insufficiently sensitive to distinguish between primary asymptomatic rubella and reinfection. The development of sensitive assay methods such as immunofluorescence (IF) and antibody-class capture and avidity provided the means for distinguishing between reinfection and primary rubella [21]. In two prospective studies carried out in the UK in the 1980s, a total of 40 babies whose mothers had reinfection during pregnancy were serologically examined [22, 23]. The maternal diagnosis was established by demonstrating a rise in pre-existing IgG antibody with a negative or low level IgM response. No evidence of congenital infection was found in any of the 40 children; in contrast 3 of 6 children whose mothers had primary asymptomatic rubella were infected [22]. Although these results indicate that the risk to the fetus of maternal reinfection is relatively low, 12 cases of congenital infection resulting from confirmed maternal reinfection have nevertheless been reported in the UK [24]. During 1987–9, 6 of the 64 (9%) cases of congenital rubella reported to the NCRSP were the result of confirmed maternal reinfections [9].

Because of the need to obtain a more precise estimate of risk, a further prospective study of the outcome of confirmed reinfection in pregnancy has been set up by the PHLS. Maternal reinfection is diagnosed either by the characteristics of the serological response at the time of infection or if there is acceptable documentary evidence of pre-existing antibody. The latter requires at least two prior antibody-positive laboratory reports by a reliable method, or a documented history of rubella vaccination followed by at least one positive antibody report [25]. Results to date suggest that the risk of fetal infection is greater than previously reported, and may be as high as 8% following maternal reinfection during the first 12 weeks of pregnancy [26]. With the success of the recently introduced MMR vaccination programme, however, few cases of maternal reinfection are now being diagnosed as exposure during pregnancy has dramatically declined.

PROSPECTS FOR THE ELIMINATION OF CONGENITAL RUBELLA IN THE UK

As a result of the co-ordinated efforts of virologists and epidemiologists in the 29 years since rubella virus was isolated, and epidemiology of the disease and the consequences of infection in pregnancy are now well understood. Much of the fundamental epidemiological research has been carried out in the UK, where the network of PHLS laboratories provides the necessary virological basis for such studies. The PHLS has also allowed the effect of selective vaccination on rubella susceptibility and infection in pregnancy to be monitored by collating the results of routine antibody screening and diagnostic testing at the CDSC. Laboratory

data, together with figures for rubella-associated terminations of pregnancy and births of congenitally-infected children, have confirmed the effectiveness of the selective programme in reducing the incidence of CRS, but have also shown the need for a combined programme if elimination is to be achieved. Just over 2 years since the introduction of MMR vaccination there are already encouraging signs that elimination of congenital rubella is a realistic target for the UK.

To guide the MMR programme towards this goal, continued surveillance of vaccine uptake, rubella susceptibility and the incidence of acquired and congenital disease is essential. Of particular importance is the surveillance of susceptibility in pregnant women in order to assess whether the current high level of selective rubella vaccination is maintained in the future. Continued surveillance of susceptibility in the general population [5] is also important not only to assess the direct effect of MMR vaccination in the younger age-groups, but also to assess the indirect effect in older unvaccinated cohorts who are now more likely to escape infection because of decreased exposure. While the endemic circulation of rubella virus continues, there may be a risk of future outbreaks in groups containing a high proportion of young adults, such as hospital staff or college students. However, the comprehensive surveillance systems in place in the UK should allow early preventive action to be taken, for example an intensive vaccination campaign targeted at susceptible groups or the introduction of a national two-stage MMR vaccination programme. With prompt and co-ordinated action by the public health services, elimination of both acquired and congenital rubella could be achieved in the UK by the year 2000.

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