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The seroepidemiology of rubella in western Europe

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SUMMARY

Most of the countries in western Europe have now implemented mass infant rubella immunization programmes, instead of or in addition to selective vaccination in order to achieve the elimination of congenital rubella syndrome.

The European countries Denmark, England and Wales, Finland, France, Germany, Italy and the Netherlands undertook large, national serological surveys collecting several thousand serum specimens during 1994–8. Antibodies against rubella virus were detected by a variety of enzyme immuno-assays. Comparability of the assay results was achieved by a standardized methodology. The age- and sex-stratified serological results were related to the schedules, coverage of rubella vaccination and the incidence in these countries.

The results show widely differing levels of immunity to rubella both in the general population and in the specific age groups of males and females. A low rate ($< 5\%$) of susceptibles in childhood and adolescents of both sexes was obtained only in Finland and the Netherlands.

Countries such as Italy with only moderate coverage for the infant immunization programme currently have both high susceptibility levels in the general population and in the at-risk population. The likelihood is of continued epidemics of rubella with cases of congenital rubella syndrome. The continued implementation of selective vaccination will help to offset the impact of this ongoing transmission and to protect women on reaching childbearing age.

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INTRODUCTION

Rubella was mainly an infection of childhood in the pre-vaccination era, resulting in a mild, febrile exanthema usually of little clinical significance, with 10–15% of adults remaining susceptible. The potential devastating consequences of infection became apparent with the realization that infection of gravid women, particularly in the first trimester of pregnancy, resulted in miscarriage or serious foetal anomaly in a large proportion of cases [1]. These anomalies were collectively termed the congenital rubella syndrome (CRS) and included sensi-neural deafness, mental retardation, heart defects and ocular abnormalities. The public health importance of CRS became apparent following the global rubella pandemic in 1962–5, with 20000 cases of CRS in the USA alone [2].

The control and elimination of CRS became possible with the licensing of several live, attenuated rubella vaccines in many industrial countries in the early 1970s. Two main vaccination strategies (or a combination of the two) have been used to protect the at-risk population. Selective vaccination of adult and/or adolescent women (providing direct protection) or mass infant vaccination designed to interrupt rubella transmission and providing indirect protection to pregnant women regardless of vaccination status as well as direct protection to the vaccinated cohorts. However, a reliance on infant vaccination can theoretically cause an increase in cases of CRS as intermediate or low levels of coverage allow continued virus circulation, with an increase of the average age at infection towards the at-risk age groups [3].

Most European countries initially adopted a selective vaccination policy for fear of waning vaccine-derived immunity. However, even with high levels of coverage, selective vaccination can still result in a small number of cases of CRS due to primary vaccine failure and the difficulties in achieving universal coverage in nulliparous women. Thus, with the availability of the combined measles, mumps and rubella (MMR) vaccine in the 1980s, and a general overall improvement in vaccination coverage, most western European countries introduced mass childhood vaccination strategies [4–6], in place of, or in addition to, their selective programme. This was in an attempt to achieve control through elimination of rubella circulation.

The WHO Regional Committee for Europe has established a target that all countries in the region should have a CRS incidence level below 0·01 per 1000 live births by the year 2010 [7]. The operational targets have been defined as vaccination coverage for mass infant immunization of at least 90%, supplemented with effective rubella and CRS surveillance. Incidence data, however, can be difficult to collate and compare between countries as the quality of CRS and postnatal rubella surveillance data varies and a substantial proportion of infection remains sub-clinical [8]. Seroepidemiological studies have attempted to overcome these problems as this approach directly describes the pattern of immunity to rubella in different populations. Unfortunately, study comparability is often limited as a variety of methodologies have been used to collect and test surveys [9]. Two types of survey have generally been undertaken: serological surveys of women of childbearing age to determine the risk of infection of pregnant women and age-stratified serosurveys which enable the prediction of the effect of various vaccination strategies [8].

The European Seroepidemiology Network (ESEN) [10] was established in 1996 to undertake standardized, comparable serosurveys for a variety of vaccine preventable infections within several European countries. The project has involved the gathering, and testing of large banks of sera, the standardization of their results and the collection of data on vaccination programme structure and historical case notifications. This article describes the current and past epidemiology and control of rubella in western Europe and identifies the optimal approaches to achieving the WHO target of elimination of CRS.

METHODS

Sera collection

Between 1994 and 1998 seven countries undertook the collection of several thousand sera specimens representative of general population: in Denmark, France, Italy, Finland, Germany, the Netherlands and the UK. The minimum number of sera to collect per age group was determined from power calculations using age-specific estimates of antibody seroprevalence. The proposed number of sera to collect was 100 from each yearly age class from 0 to 19 years, 200 from each five yearly age class from 20 to 39 years, 200 sera from each 10-yearly age class from 40 to 59 years and 200 sera from those 60 years of age or greater. The total proposed number of sera was

therefore 3400. The actual total number of sera collected varied between 2766 and 8306.

The method of sampling used by each country has been described previously [11]. Two sources of sera were used: population based random sampling or residual sera collected during routine laboratory testing. The only exclusion criterion for samples was sera from individuals with known immune deficiency. Samples were collected from a variety of geographical locations within each country to provide a reasonably representative estimate of the general population. For each specimen, the age, sex, year of collection and some regional data were gathered. In the following analysis results from the former East and West Germany were divided as they had different vaccination histories. Because of previous reports of regional variation in vaccine coverage in Italy, data was split into North (comprising Lazio and all regions North of this) and South (consisting of Abruzzi and all regions South of Lazio including Sardegna).

Standardization and panel testing

Seven countries undertook rubella antibody testing in a designated national laboratory with their usual enzyme immuno-assay (EIA)[12]. Denmark, Finland, France, Germany and Italy used Behring (Enzygnost®), the Netherlands an inhouse assay and the UK, Microgen. To achieve quantitative comparability of assay results between countries, the results were standardized using a methodology developed as part of the ESEN project. This has been described in detail previously [12]. Briefly, the process involved the distribution of a panel of more than 100 negative, low positive and positive sera by the reference laboratory (Preston Public Health Laboratory, UK) for testing in the national laboratories of the other participating countries. The local results of panel testing in these countries were regressed against those of the reference laboratory to develop standardization equations.

Main serosurvey testing

The main serosurveys were tested using the same validated EIA assays as the reference panel. The standardization equations were used to convert the local quantitative results of testing the main serosurveys into standardized reference laboratory units. The reference laboratory cut-off range was used to classify all countries standardized quantitative values into qualitative results (negative < 4 IU, low positive 4–10 IU, positive > 10 IU). Unless otherwise stated, low positives were reclassified as positive. As detailed in a paper describing the standardization process, these values are at variance with the unitages produced by other EIAs, thus the results reported in this paper may differ slightly from percentages reported by individual countries elsewhere.

Coverage estimation

A number of countries had inadequate or incomplete coverage data for both the selective and mass (infant) programmes. However, the serological results allowed estimates of coverage for selective vaccination and MMR vaccination to be made [13]. This method utilized serological data at the individual level to estimate the proportion of individuals of a given age who have been vaccinated as well as the proportion infected with each of the three viruses. By assuming that seroconversion to each of the three antigens is independent within an individual and that the viruses circulate independently of each other (so the chances of being infected are independent), then the probability of an individual of a given age being in any of the eight mutually exclusive serological groups (ranging from positive to all three to negative to all three) can be described in terms of vaccine coverage (in that cohort), vaccine efficacy for each of the three components of the vaccine, and the cumulative infection rates. These parameters are then estimated using maximum likelihood.

The proportion of girls who have received selective rubella vaccination can be estimated from aggregated serological data, which is separated by sex (that is, unlike the above technique it is not necessary to have individual level data). Assuming males and females of a given age mix equally with each other and that there are no intrinsic sex differences in response to infection or vaccination implies that any observed sex difference in prevalence of antibodies is due to the selective programme. This allows an estimation of the past coverage level of any selective programme, using the following formula:

$$C_i = 1 - \frac{Q_{if}}{Q_{im}},$$

where the C_i is the estimated effective coverage in each age cohort i and Q_{if} and Q_{im} are the proportion of females and males in age group i who are seronegative. The mean coverage for the selective campaign can be obtained from the average of the $C_i s$. For instance, if

there is serological evidence of a significant difference in antibody prevalence in 13–23 year old females compared to males, this suggests that a selective programme of 13 year old girls had been in place for 10 years. Alternative explanations are possible, for example a recent one-off campaign targeted at 13–23 year old females. We used the official coverage data and recommendations to determine the most likely scenario. If there was any doubt, we assumed that successive cohorts had been vaccinated, rather than wider age-bands over a shorter time period.

Note that if any boys in the target age cohorts had been vaccinated then the proportion of girls immunized in the selective programme will be underestimated using the above technique.

Vaccine programme structure and coverage

As part of the project, a questionnaire was completed by each participating country on country-specific information on rubella vaccine programme structure, historical vaccine coverage and reported incidence of rubella infection and cases of CRS (see also [14]).

RESULTS

All seven countries have now implemented national mass infant immunization programmes, with only one, Italy, also maintaining a 'mass' selective schoolgirl programme (Table 1). We divided these countries into three groups according to the proportion of the population susceptible to rubella infection amongst adolescent females (Fig. 1b). This was related to each country's vaccination programme. Finland, the Netherlands and England and Wales were in the low susceptibility group (proportion susceptible to rubella $< 5\%$); Denmark and Germany in the moderate susceptibility group (proportion 5–10%); France and Italy in the high susceptibility group ($> 10\%$). The population age-specific seroprofile for rubella antibody seropositivity and the estimated proportion vaccinated for each country is shown in Figure 2.

Finland

In Finland, the serological survey was conducted in 1997–8. Selective vaccination was introduced in the early 1970s and then stopped in 1989 after the introduction of infant mass vaccination in 1982 (Table 1). The seroprofile shows very low levels of susceptibility in all age groups over the age of one year (Fig. 2), reflecting the relatively long history of rubella vaccination in Finland with high levels of coverage [14, 15]. For the older age groups (more than 35 years), seropositivity largely corresponds to naturally acquired infection from the pre-vaccination era. With the interruption of endemic rubella transmission (the annual reported incidence of rubella has been below 1/100000 since 1992) (Fig. 3), the vast majority of those between the age of 1 and 25 years, have vaccine-induced protection. This may account for the relatively high proportion of low-positives observed in the adolescent age classes – comparing the Finnish seroprofile with those from other countries (Fig. 2). The higher proportion of women with antibodies to rubella aged 20–39 years (99%) compared with males in the same age group (96%) is a historic reflection of selective vaccination (Fig. 1).

The Netherlands

The seroprofile was undertaken in 1995–6, approximately 8 years after two-dose MMR vaccination replaced selective vaccination of pre-adolescent girls in the Netherlands (Fig. 2). The high levels of coverage achieved with both these strategies has resulted in a low proportion of the population being seronegative, with over 95% of those above one year of age estimated to be seropositive and approaching 100% in teenagers. Laboratory confirmed cases of rubella continue to occur in the Netherlands (Fig. 3), though at low levels. Thus the majority of those under the age of about 17 years are likely to have vaccine derived, rather than naturally acquired protection (Fig. 2). Most of those above 35 years of age are likely to have naturally acquired immunity. A very low proportion of females of childbearing age are susceptible: 5/455 of those aged 15–19 years and 2% of those aged 20–39 years were estimated to lack antibody to the rubella virus (Fig. 1). For children over the age of 2 years, the proportion seropositive exceeds the estimated proportion vaccinated. This may be due to chance, or be indicative of natural infection, though the proportion with natural immunity is likely to be extremely small. An alternative explanation is that those who were vaccinated were more likely to participate in the population-based serosurvey.

England and Wales

The results of the serosurvey, undertaken in 1996, 9 years after the introduction of mass MMR vaccination and 2 years after the MR campaign targeted at 5–16

Table 1. *Evolution of monovalent rubella vaccination programmes in seven countries participating in the ESEN-project from introduction to current status*

Country	Adolescent schoolgirl programme	Target female population (age in years)	Current antenatal screening programme
Denmark	No	—	
England and Wales	1970–93	11–14	Yes
Finland	1975–89	13	No*
Former East Germany	1991–7	11–15	Yes
Former West Germany	1975–97	11–15	Yes
France	1970–83	11–13	Yes
Italy	1973–	Adolescent	Yes
The Netherlands	1974–87	11	No

* Ended 4 years ago.

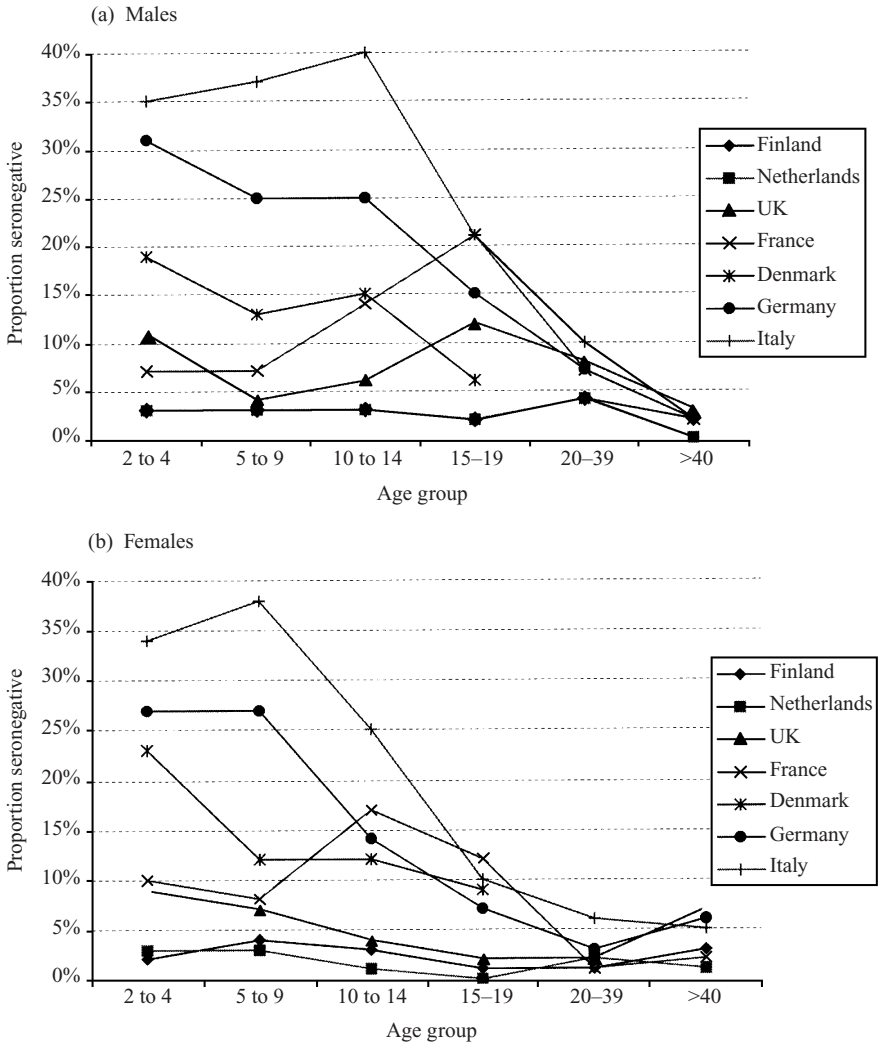

Fig. 1. Percentage of population seronegative for rubella antibodies by age-group and sex in countries involved in the ESEN project.

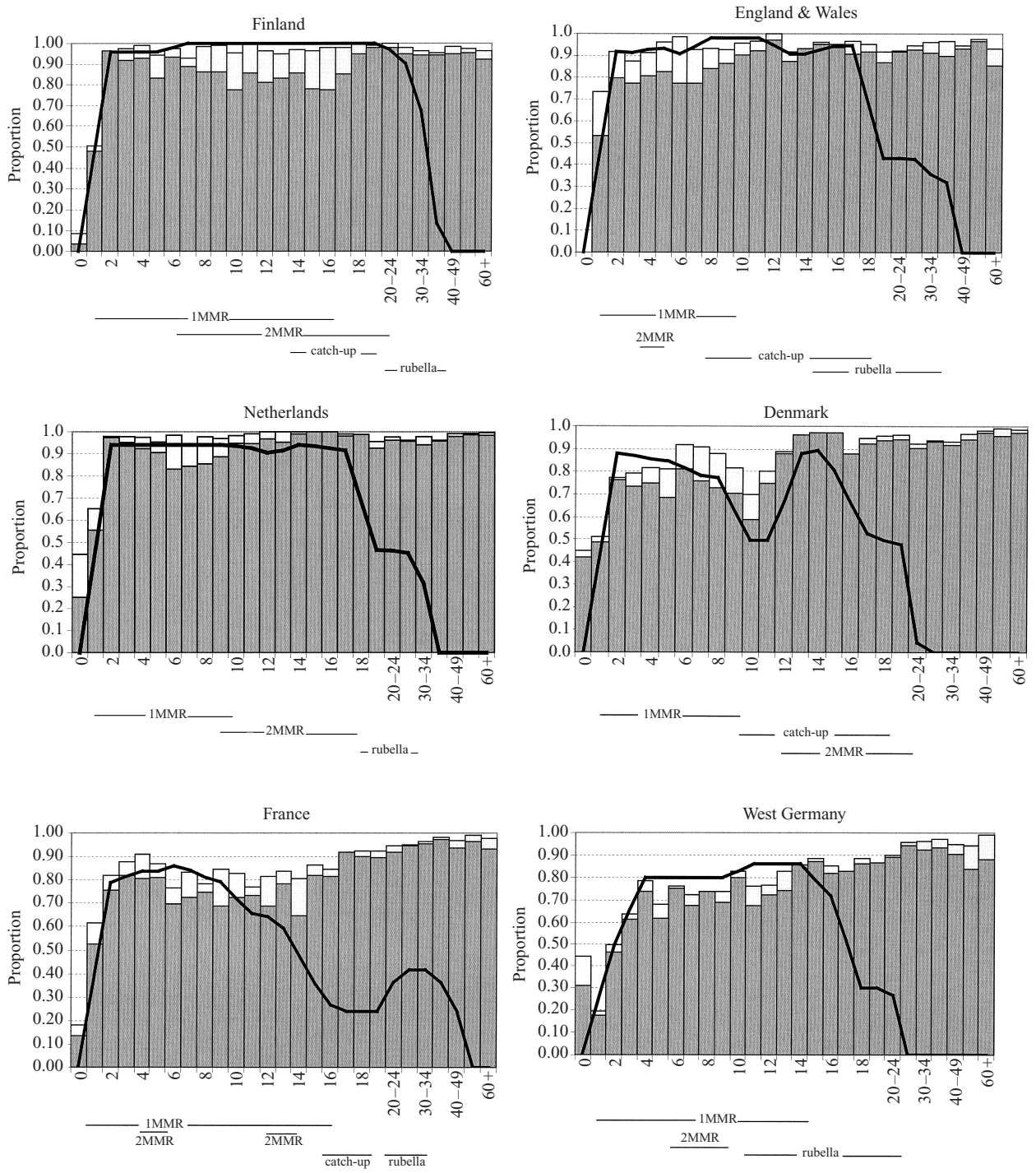

Fig. 2. For legend see facing page.

year olds, show that in England and Wales the prevalence of rubella antibodies was above 90% in all age groups greater than 3 years of age (Fig. 2). The proportion of females of childbearing age estimated to be seronegative to rubella was low at 2% aged 15–19 years and 2% in those aged 20–39 years (Fig. 1). This compares with a relatively high proportion of seronegative males in these age groups (12% and 8% respectively). In 1996, 2776 laboratory confirmed cases of rubella were reported in England and Wales, 95% of which occurred in individuals older than 14 years of age, of whom the majority were male [16] (Fig. 3). The incidence rate of infection in pregnant women in this year was 5/100000 pregnancies.

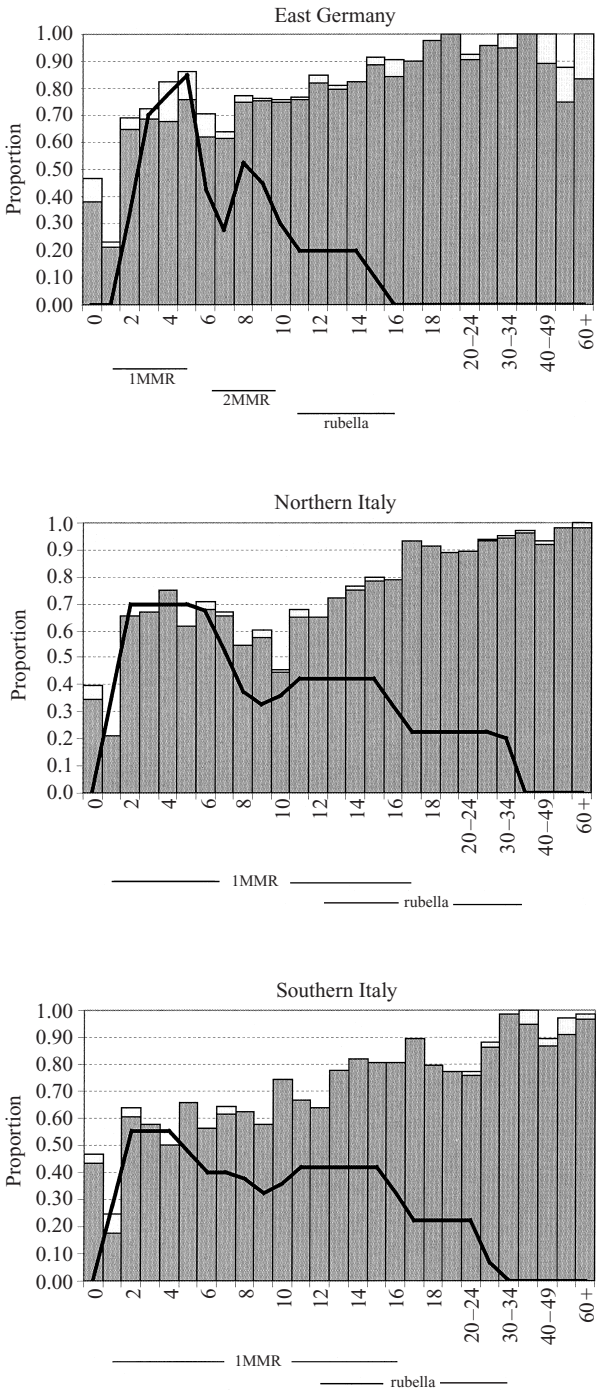

Fig. 2. Seroprevalence of rubella antibody for each ESEN member country, and estimated proportion of each age-group vaccinated (—). (■, positive; □, low positive) and their vaccine history; (Age-group vaccine history defined below each figure: rubella (adolescent/adult female selective vaccination programme), MMR1 (single dose mass infant vaccination programme), MMR2 (second dose mass vaccination programme), catch-up (one-off targeted vaccination programme)).

Denmark

Denmark first introduced rubella vaccination (as a two-dose MMR programme) in 1987 along with a catch-up campaign for adolescent girls. The samples in Denmark were collected at two points in time, complicating the interpretation of the serological profile (Fig. 2). Those under the age of 7 years were sampled in 1998, all other age groups were sampled during 1994–5. Nevertheless, it is evident that during 1994–5 there was a significant trough in the proportion with serum antibodies to rubella in the 9–11 year age group (the second dose of MMR is given at 12 years of age). Although epidemics have ceased to occur, wild virus still circulates in Denmark (Fig. 3). The reported incidence of rubella remained above 1/100000 in 1993 and from 1994–6, 13 cases of infection amongst pregnant women have been reported (5 cases/100000 pregnancies/year [17]).

Germany

There are historical differences in rubella vaccination history between the former East and Western parts of the country. In West Germany, selective rubella vaccination was introduced in 1975, followed by the addition of mass infant single dose MMR programme in 1980. However, prior to reunification rubella vaccination was not routinely offered in East Germany (only to seronegative women working in kindergardens and children's hospitals). In 1991, a two-dose MMR programme was introduced in the whole country, with the second dose targeted at 6 year olds. Since 1998 vaccination of teenage girls is only recommended for those without documentary evidence of two previous doses of MMR.

The serological survey was undertaken in 1995. In both East and West Germany, coverage of the first dose of MMR has been relatively high (reaching around 80%), but uptake appears to be spread over the first 4–5 years of life (Fig. 2). Uptake of the second dose at 6 years of age appears to be low [13]. The comparatively slow uptake of MMR accounts for the comparatively slow rise in those with serological evidence of immunity to rubella over the first few years of age when compared with the other countries. The lower levels of coverage, both current and historical, results in a larger proportion of individuals being seronegative for rubella antibodies as compared with the previously discussed countries. In West Germany, roughly 25% of children aged 5–13 years are estimated to be seronegative to rubella. The

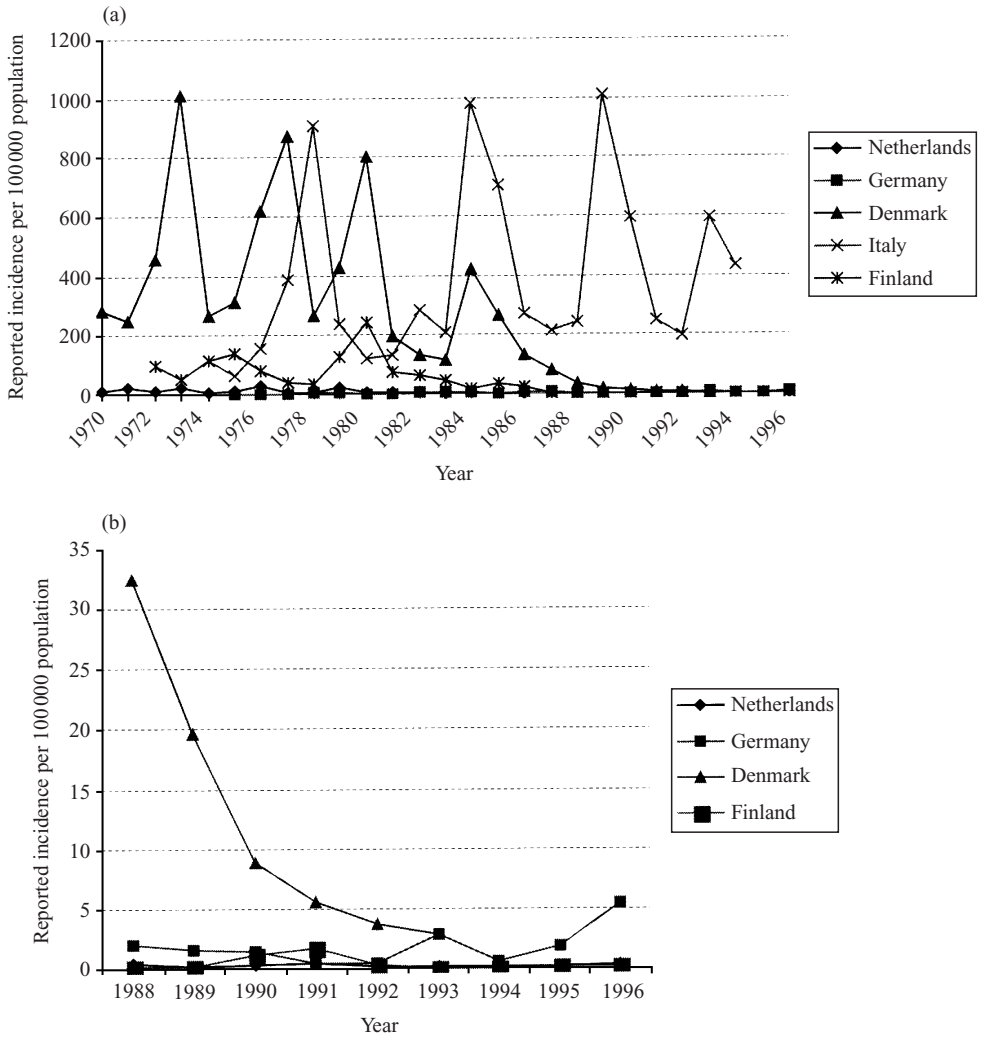

Fig. 3. Reported incidence of rubella case notifications per 100000 population in five countries involved in the ESEN-project.

gradual rise in seropositivity in adolescents and young adults is evidence of probable continued viral circulation in these age groups (Fig. 2). It is likely that cases still arise in pregnant women as roughly 8% of 15–19 year old and 3% of 20–39 year old women were seronegative for rubella antibodies. This compares to the higher levels of 20% and 8% respectively of men in the same age groups. This difference is a historical reflection of the protection afforded by selective vaccination. As in other countries, there is a tendency for those age cohorts which have experienced low (or zero) coverage levels to have a smaller proportion of low positives (with the exception of the elderly) (Fig. 2). This demonstrates the higher antibody titres associated with naturally acquired immunity.

In East Germany, most of those with antibodies to rubella would have acquired these via natural infection, with the exception of children 2–6 years of age. Levels of susceptibility in school-aged children are similar in the former East Germany to the western part of the country (Fig. 2). The proportion of women aged 15–19 years who were seronegative was 7% and 5% for women age 20–39 years. A similar proportion to males of the same age group (8% and 5% respectively) and a reflection of the lack of a selective vaccination programme.

France

The serological survey was undertaken in 1998 (Fig. 2). Selective rubella vaccination was introduced in 1970, targeted at adolescent girls (Table 1). With the introduction of single dose MMR vaccination in 1983 for infants, vaccination of unimmunized teenage girls and women of childbearing age was kept in the immunization schedule. The selective vaccination of

all girls at 11–13 years was replaced by vaccination of both sexes with a second dose of MMR introduced in 1996. The age of the second dose was shifted to 3–6 years in 1998, a catch-up for all unimmunized children aged 11–13 was maintained, and also for unimmunized women above this age.

Although the prevalence of rubella antibodies was greater than 80% for children aged 3–6 years, consistent with recent higher vaccination coverage, for those aged 7–13 years, seropositivity remains only around 80%. Seropositivity only rises above 90% by the age of 18 years. Worryingly, it can be seen (Fig. 1), that there is still a substantial pool of susceptible teenage girls (17% of 10–14 year olds and 12% of 15–19 year olds) and boys (14% and 21% respectively). With the cessation of selective vaccination and the shift in the age of the second dose to 3–6 years of age, and reliance on screening for unimmunized women, this pool of susceptibles potentially remains at risk of infection.

The number of reported cases of rubella in pregnancy in France has declined from 309 cases in 1984 to 28 in 1992, although there are still regular peaks (the last in 1997, with 84 infections) indicating that wild virus continues to circulate (the last figure corresponding to a risk of 10·8 per 100000 pregnancies).

Italy

Selective rubella vaccination of adolescent females was introduced in 1973 and still remains in place. Single dose MMR vaccination for infants was introduced in 1979 with coverage by region varying greatly from 26 to 88% in 1998 [18].

The serosurvey collected in 1996–7, suggests that there are relatively high levels of susceptibility in Italy in all but the oldest age groups (Fig. 2). This is consistent with the low levels of coverage achieved in Italy compared with the other countries and the apparent lower force of infection in Italy than in many other countries [19]. The higher level of infant MMR coverage in Northern Italy results in somewhat higher levels of seropositivity in children under the age of 10 years compared with the South. Likewise the selective vaccination programme (which appeared to have negligible levels of coverage in the South until the early 1980s (Fig. 1) may have contributed to the lower level of susceptibility in women of childbearing age in the North compared with the South. Nevertheless a large proportion of women of childbearing age remain unprotected from rubella infection (6% of 15–39 year olds in the North and 12% of 15–39 year olds in the South, which compares with 13% and 18% respectively, of men of the same age). The continuing rise in seropositivity in these at-risk age groups is evidence of continued infection in adults. Indeed, endemic rubella transmission continues in Italy, with epidemics every 6–7 years (the last in 1993) (Fig. 3) with concomitant increases in the number of reported cases of CRS.

DISCUSSION

Seroepidemiology can play an important role in evaluating the impact of rubella vaccination programmes; both rubella and CRS notification data have well described limitations. They can be unreliable due to both underdiagnosis (up to 50% of acute cases are estimated to be sub-clinical) and under-reporting of clinically apparent cases. However, to undertake a formal comparison of the serological surveys from different countries requires the development of standard methods: large, finely age-stratified samples, similar assay methods and standardization of the results against a reference panel using the same cut-off levels. The subsequent serological profiles can thus provide a comparable estimate of susceptibility levels both in the general population and the at-risk group – women of childbearing age. The standardization of these parameters has enabled a direct evaluation of the impact of the rubella vaccination programmes in each of the ESEN countries.

The current population susceptibility levels seem to be influenced by a number of factors: the year of introduction of the vaccination programme, the target population, the age at vaccination, the number of doses given, the level of vaccine coverage and exposure to wild virus. All countries (except Denmark and East Germany) initially introduced selective vaccination programmes targeted at adolescent girls during the 1970s. These were implemented with varying degrees of success, reflected by the proportion of women of childbearing age currently susceptible to rubella, varying from 1 to 6% amongst women aged 20–39 years and from 1 to 12% amongst teenagers aged 15–19 years. Rubella virus continued to circulate amongst children and CRS cases occurred at an unacceptably high rate [20]. Thus with the development of MMR vaccine, Finland in 1982, followed by the remaining ESEN countries, introduced mass

childhood vaccination aiming to interrupt rubella virus circulation and eventually achieve CRS elimination. Success however has been mixed.

The very low susceptibility countries, Finland and the Netherlands, both introduced two-dose MMR programmes with high vaccine coverage during the early 1980s. This has had a dramatic effect on population seroprofile. In Finland, during the pre-vaccination era, only by the age of 15 years were over 90% of the population immune. The introduction of the two-dose MMR programme with over 95% coverage in 1982 has resulted in excess of 90% of those over the age of 1 year being immune, interrupting viral transmission. Furthermore, susceptibility levels amongst adult women were also very low, a reflection of the selective vaccination programme stopped in the 1980s. In the Netherlands, a small number of cases of rubella infection still occur each year, including infections of pregnant women. This disparity compared to Finland could be related to a higher rate of importation in the Netherlands into geographic clusters of unvaccinated individuals. Outbreaks of rubella have been documented amongst religious groups previously, such as the Amish in the USA [20, 21].

Success was less marked in those countries, which initially introduced single dose MMR programmes at lower coverage levels. Some continued their adolescent rubella vaccination programme (England and Wales) in a mixed policy, others (France) relied on the infant programme and stopped the adolescent programme, and others had no selective programme (Denmark). Thus in England and Wales, only a large pool of teenage males remained susceptible until the introduction of the MR campaign in 1994, whereas in France and Denmark both teenage girls and boys remain susceptible. There remains a continued potential for rubella epidemics amongst these groups. Indeed in France, outbreaks of rubella amongst adults of both sexes with cases of CRS have already been documented [22]. This mirrors the experience in Greece, where the introduction of infant immunization with inadequate coverage, with the lack of a policy for vaccinating adolescent females, was followed by a major rubella epidemic. This affected women of child-bearing age at higher rates than previously recorded [23].

In Italy, there has been continued rubella transmission, as childhood vaccination coverage levels have been inadequate to interrupt transmission. Furthermore, there is substantial regional variation in susceptibility levels between North and South amongst adult women aged 15–35 years, reflecting regional variations in vaccine coverage. The current moderate/low coverage for infant rubella immunization has also resulted in an upward shift in the average age of infection [24]. Fortunately, Italy has continued a policy of selective adolescent vaccination, which will have provided some protection.

The age distribution of low positives suggests a concentration in cohorts with vaccine derived immunity. In low susceptibility countries with little or no natural boosting, there is evidence of an increasing proportion of low positives in the vaccinated cohorts with increasing age. This may indicate waning vaccine induced antibody titres compared with naturally acquired immunity. The biological significance of this observation in terms of protection is unclear, as other parameters such as cell-derived immunity, also probably play an essential role in providing protection. Previous studies have generally concluded that vaccine-derived protection is lifelong [25, 26], although occasional cases of CRS have been reported due to secondary vaccine failure [27]. In those countries near to the elimination of rubella, with a consequent reduction in natural boosting of vaccinated cohorts, continued monitoring of population susceptibility levels will be important.

In conclusion, several countries with well-organized vaccination programmes have achieved the population susceptibility levels required to interrupt transmission and reach the CRS incidence targets established by the WHO. With the closure of population immunity gaps, many have now stopped their schoolgirl immunization programmes and reliance has been placed on the two-dose MMR programmes. The priority will be to maintain high coverage levels for these programmes, supported by high quality, sensitive laboratory surveillance. Regular serosurveys will be needed to detect any potential immunity gaps or evidence of waning immunity. Some of the moderate susceptibility countries despite implementing mass vaccination with one or two dose programmes still have large pools of susceptibles. It is important to ensure immunization strategies are in place to protect women of childbearing age, whether through one-off campaign or routine 'selective' vaccination with or without routine antenatal screening. Countries such as Italy with only moderate coverage for the infant immunization programme currently have both high susceptibility levels in the general population and in the at-risk groups, with wide regional variation in susceptibility levels. Continued transmission of rubella with cases of CRS is

inevitable. The continued implementation of selective vaccination helps to offset the impact of this ongoing transmission. An increase in MMR coverage in all regions is required, in addition to maintaining the selective schoolgirl vaccination programme and/or antenatal screening to continue to protect women on reaching childbearing age.

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