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Increase of immunity to rubella and interruption of rubella transmission in Gipuzkoa (Basque Country, Spain) after an enhanced vaccination programme

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SUMMARY

In Spain, vaccination against rubella was initiated in schoolgirls in the mid-1970s. In Gipuzkoa, subsequent extensions to the vaccination schedule culminated in 1992 with the introduction of the two-dose measles, mumps and rubella vaccine in children and adolescents of both sexes. Moreover, in 1985 a programme for the identification and vaccination of non-immune parturient women was implemented in the region's main hospital. The prevalence of rubella-susceptible parturient women decreased from 3·7% at the beginning of the study to $<1·5$% by 1992. Despite this overall decrease, 4·8% of adolescent parturients were susceptible to rubella during 2001–2002. From 1984, the number of reported cases of rubella (children and adults) progressively decreased until 1997, after which there have been no cases of indigenous rubella. There have been no cases of reported congenital rubella since 1984. These results indicate that the vaccine policy carried out in this geographical area has been effective in achieving considerable progress towards rubella elimination.

INTRODUCTION

When rubella occurs outside pregnancy, it is usually a mild disease that only rarely presents complications. However, infection during early pregnancy may cause foetal death or congenital rubella syndrome (CRS). Because of the frequency of CRS in rubella epidemics and the severity of its sequelae (such as deafness, heart disease, cataracts and mental retardation), the disease represents an important threat to child health globally [1–3]. The rubella vaccine is effective and well tolerated, and its use has reduced the incidence of rubella and CRS [1, 3–5]. The main reasons for the different epidemiology of rubella in countries with immunization programmes against this infection are differences in the vaccine strategies applied, the length of time since their implementation, and the vaccine coverage achieved [6].

Rubella vaccination was introduced in Gipuzkoa in 11-year-old girls in 1977 [7]. Measles, mumps and rubella (MMR) vaccination was introduced in children of both sexes aged 12–15 months in 1981. At the same time, the selective vaccination of seronegative women of childbearing age was recommended [8], although no specific programme was implemented. To accelerate rubella control, a programme for the detection and vaccination of non-immune parturient women was introduced in Donostia

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Hospital in 1985. This programme facilitated longitudinal serological surveillance for more than 17 years. In the 1991–1992 school year, a second dose of MMR was introduced to 11-year-olds of both sexes, substituting selective vaccination against rubella for girls. In 2000, the age at which the second dose of MMR was administered was brought forward to 4 years and a catch-up vaccination campaign was performed in children aged 5–11 years. The rubella vaccine strain used in Gipuzkoa throughout these years was RA27/3.

In the present study we report changes in rubella immunity and incidence in the population of Gipuzkoa and discuss the role of the vaccination policies in these changes. In addition, we have evaluated the programme for the detection and vaccination of non-immune parturient women.

METHODS

Gipuzkoa is one of the three regions comprising the Autonomous Community of the Basque Country, northern Spain (1997 km² and 676 208 inhabitants). Donostia Hospital is the main hospital in Gipuzkoa and attends approximately 65% of women who give birth in the region. Between August 1985 and December 2002, all of the women giving birth at Donostia Hospital were included in the programme for the detection of non-immune parturient women.

Vaccination coverage and data on incidence

Vaccination coverage levels were calculated for in the following time periods:

(1) One-year-old children (first dose of the MMR vaccine) – from 1984 to 2002.
(2) Eleven-year-old girls (rubella vaccine) – between 1984 and 1991.
(3) Eleven-year-old adolescents and 4-year-old children (second dose of the MMR vaccine) – between 1992 and 1999 and between 2000 and 2002 respectively.

The number of children and adolescents vaccinated were obtained from public health services records, where each vaccination is documented. The total number of 1-year-old children to be vaccinated was obtained from the Metabolic Diseases Detection Programme of the Autonomous Community of the Basque Country, being this number the number of those born in Gipuzkoa in the previous year. In the other age groups the number of children and adolescents to be vaccinated were obtained from the corresponding population census (Basque Institute of Statistics). Data on the annual incidence of rubella in the region were obtained between 1984 and 2002 from mandatory infectious disease reports sent each week to the Notifiable Disease Reporting System by general practitioners and paediatricians. To detect cases of CRS, data from the Congenital Anomalies Register of the Autonomous Community of the Basque Country, in operation since 1990 and included in the EUROCAT (European Surveillance of Congenital Anomalies) network, were used. Before 1990, cases of CRS were obtained through the registers of all the paediatric hospitals of the region and from the Prosubnormal Association of Gipuzkoa [9]. The Microbiology Laboratory of Donostia Hospital is the reference laboratory for serological confirmation of rubella cases in Gipuzkoa.

Prevalence studies

The prevalence of rubella immunity was studied in two population groups.

Group I comprised women who gave birth in Donostia Hospital between August 1985 and December 2002. These women came from throughout the region of Gipuzkoa and were from all social classes, including the most disadvantaged socioeconomic groups. Serum samples were obtained from all women admitted for delivery and tested for antibodies against rubella. Women considered non-immune were offered vaccination before leaving the hospital.

Group II was composed of 1151 children and adolescents aged between 2 and 13 years from whom blood had been obtained during 1994–1995 for the diagnosis of mild, non-exanthematous diseases (before minor surgery, gastroenteritis, etc.). These children and adolescents were treated as outpatients and most were from the city of San Sebastián (the capital of Gipuzkoa) and did not have known immunodeficiencies. The number of children and adolescents analysed in each age group varied between 68 (in the group of 7-year-olds) and 151 (in the group of 13-year-olds). Serum samples were stored at −40 °C until processing. The results obtained in this study were compared with those obtained in another population group of 1306 children and adolescents aged between 2 and 13 years selected during 1986–1988 in the same way and from the same

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geographical area, and analysed with the same serological method [9].

Serological methods

Testing for antibodies against rubella was performed between 1985 and 1998 with the latex agglutination (LA) method (Rubascan®, Becton Dickinson, Sparks, MD, USA) using serum diluted 1:5. This method detects rubella antibody levels of approximately 10 IU/ml [9]. From 1999 the LA method was substituted by a microparticle enzyme immunoassay (MEIA) method (AxSYM Rubella IgG, Abbott Laboratories, Abbott Park, IL, USA) in which samples with rubella IgG antibody levels of 10 IU/ml or greater are considered positive. Individuals with a positive result in these serological methods with the above-mentioned cut-off values were considered immune. Women with a negative result were considered susceptible to rubella and were offered vaccination before leaving the hospital. Individuals with an equivocal result in the MEIA method (5·0–9·9 IU/ml) were tested with the LA method using serum diluted 1:5, and were considered immune if the LA method obtained a positive result. When rubella was suspected, detection of IgM antibodies against rubella was performed with a commercial enzyme immunoanalysis method (Enzygnost, Dade Behring, Marburg GmbH, Germany). Samples with an optical density (OD) $\geqslant 0{\cdot}3$ were considered IgM positive, and those in which this value was $<0{\cdot}2$, IgM negative. Specimens with an OD between 0·2 and 0·3 (equivocal results) were retested and considered IgM positive if the second OD was $\geqslant 0{\cdot}2$. Serological methods were performed at the Microbiology Laboratory of Donostia Hospital following the manufacturer's instructions.

Evaluation of the programme for the systematic detection and vaccination of seronegative parturient women

Three indices were calculated for the evaluation: the percentage of seronegative parturient women who were vaccinated before leaving the hospital, the percentage of vaccinated women who showed seroconversion (both percentages were studied between April 1987 and December 1992), and the number of subsequent pregnancies in the following 10 years in parturients identified as seronegative (for women who delivered between 1990 and 1992).

Data analysis

The χ^2 test and Fisher's exact test were used to compare prevalences. P values of $<0{\cdot}05$ were considered significant.

RESULTS

Vaccination coverage

Changes in the annual vaccination coverage against rubella and MMR were calculated from 1984 and are shown in Figure 1. The mean annual coverage for the first dose of MMR vaccine was 93·7% between 1987 and 2002, and was 90·1% for the second dose between 1992 and 2002. The coverage of selective vaccination in 11-year-old girls was >70% from 1984. Finally, the vaccination coverage achieved by the catch-up vaccination campaign carried out in 2000 in children of both sexes aged 5–11 years was 92·4% (33 541/36 293).

Incidence of rubella

Between 1984 and 2002 the number of reported cases of rubella showed a downward trend (Fig. 2) from >100 cases per 100 000 inhabitants to zero cases per 100 000 inhabitants between the first and last 2-year periods studied respectively. Two major rubella outbreaks occurred in the first 6 months of 1992 and 1996, which affected mainly teenage boys, most of whom were born between 1977 and 1982. Since 1997, no indigenous cases of rubella have been confirmed in Gipuzkoa. In this period (1997–2002) the laboratory received samples for investigation of specific IgM from 632 patients with symptoms compatible with rubella (exanthema, enlarged lymph nodes, etc.). The only serologically confirmed case occurred in a 20-year-old man who travelled to Gipuzkoa from another Autonomous Community of Spain in the initial phase of the disease in 2000. Between 1984 and 2002 no cases of CRS have been reported in Gipuzkoa.

Prevalence of rubella antibodies

Group I (*parturient women*)

Between 1985 and 2002 the prevalence of rubella antibodies was analysed in 65 329 women. Of these, 64 249 (98·3%) were immune. During 1985–1986, 3·7% of the women studied were considered to be susceptible. This percentage progressively decreased

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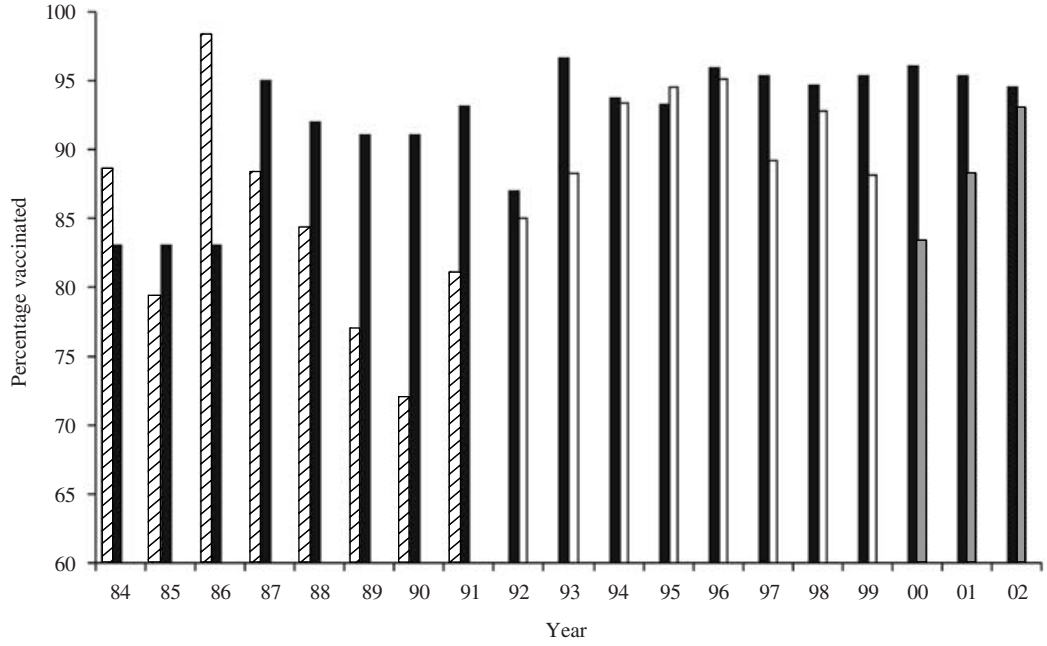

Fig. 1. Annual vaccination coverage levels of the monovalent vaccine against rubella and of each of the two doses of the measles, mumps, and rubella (MMR) vaccine in Gipuzkoa (Basque Country, Spain) between 1984 and 2002 (the vaccination strategy is described in the Introduction). ▨, Rubella (11 years old, girls only); ■, MMR1 (1 year old); □, MMR2 (11 years old); ▩, MMR2 (4 years old).

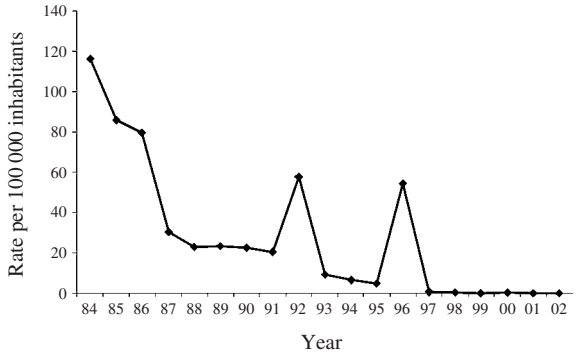

Fig. 2. Reported incidence of rubella case notifications per 100 000 population in Gipuzkoa (Basque Country, Spain), 1984–2002.

to 0·93% for 1997–1998 and then slightly increased to 1·4% for 2001–2002 (Fig. 3). The Table shows the percentage of susceptible women during 2001–2002 according to age. Noteworthy is the relatively high percentage of susceptible adolescent parturients (4·8% of those aged <20 years) compared with that of susceptible adult women (1·3% of women aged 20–49 years) (Fisher's exact test $P=0·027$).

Group II (*children and teenagers aged between 2 and 13 years*)

Of the 1151 children studied during 1994–1995, 1119 (97·2%) were immune to rubella. The percentage of immune children was >95·7% in each of the age groups studied (Fig. 4). Comparison of the prevalence of immunity in relation to sex between girls and boys aged between 2 and 10 years revealed no differences: 97·3% of girls (355/365) and 97·2% of boys (375/386) were considered immune. However, in children aged 11–13 years the prevalence of immunity was greater among girls than boys: 99·1% (214/216) and 95·1% (175/184) respectively ($\chi^2=5·84$, $P=0·015$). Comparison of the results obtained in this study with those obtained in the serosurvey analysed during 1986–1988 is shown in Figure 4. The prevalence of rubella antibodies in the group of children analysed during 1986–1988 was 78·8% (1029/1306).

Evaluation of the programme for the systematic detection and vaccination of seronegative parturient women

Of the 499 women considered non-immune between April 1987 and December 1992, 401 (80·4%) were vaccinated before leaving hospital. In 301 of these women, serum samples obtained between 30 and 50 days after vaccination showed that 288 women (95·7%) had seroconverted. Of the 125 women who were seronegative between 1990 and 1992 and who were followed-up for 10 years, 42 (34%) gave birth at least once more, with a total of 51 additional births.

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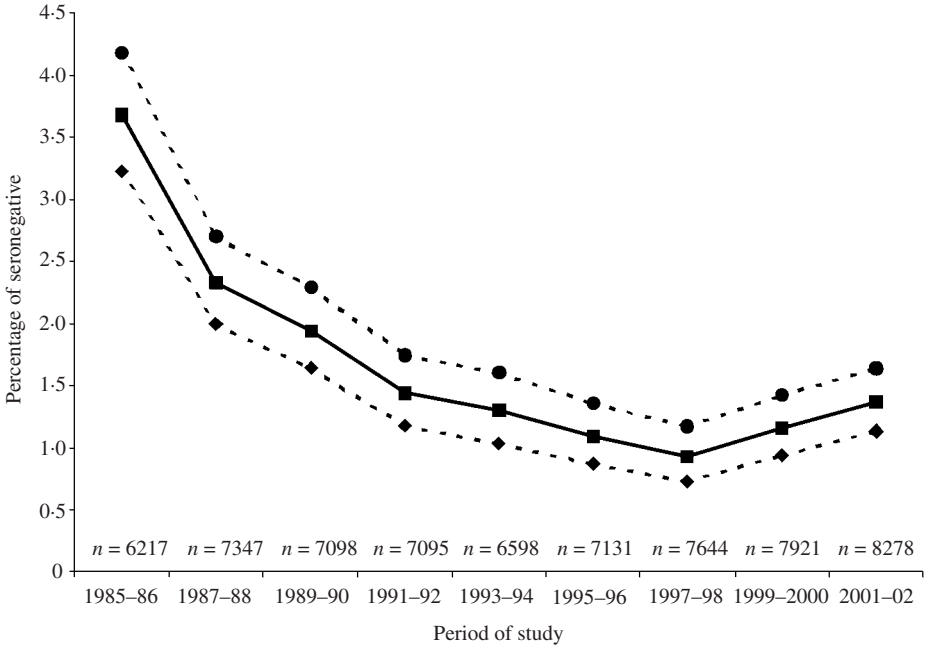

Fig. 3. Percentage of parturient women without rubella antibodies in Gipuzkoa (Basque Country, Spain) studied between August 1985 and December 2002 (middle line with squares). Upper line (circles) and lower line (diamonds) represent upper and lower exact binomial 95% confidence intervals (Epitable calculator program, Epi-Info, version 6, 1994, CDC, USA).

Table. *Percentage of women susceptible to rubella among parturient women in Gipuzkoa* (*Basque Country, Spain*) *by age group* (*period 2001–2002*)

Age (years)	Number investigated	Rubella antibody negative	
		Number	(%)
14–19	83	4	(4·8)
20–24	325	7	(2·2)
25–29	1944	31	(1·6)
30–34	3739	36	(1·0)
35–39	1913	30	(1·6)
40–49	192	4	(2·1)
Unknown	82	1	(1·2)
Total	8278	113	(1·4)

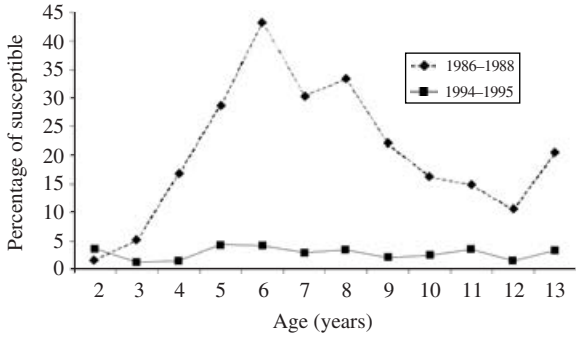

Fig. 4. Rubella susceptibility in children and adolescents aged 2–13 years from Gipuzkoa (Basque Country, Spain), during 1994–1995. Comparison with the results obtained in another population group selected in the same way and analysed with the same serological method during 1986–1988 [9].

DISCUSSION

The rubella vaccination strategies initially introduced in the countries pioneering the fight against this disease involved a single vaccine dose and focused on the immunization of children of both sexes, such as in the United States, or schoolgirls, such as in the United Kingdom [10]. These strategies were only partially successful, and since the 1980s they have been progressively replaced by the two-dose MMR vaccination strategy (such as that currently in operation in our region) in children of both sexes, which involves the administration of a first dose in infants and a second dose at school entry or adolescence. In many countries, this policy is supplemented by the vaccination of seronegative women [10, 11]. This two-dose strategy is believed to have led to the elimination of rubella in Finland [12] and Sweden [13], as well as to the low levels of circulating

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virus found in the last few years in Holland [14] and the United States [4]. Differences in the vaccine strategy or low coverage explain the less favourable results observed in other parts of Europe such as Italy [14, 15] and Greece [16], where, until recently, circulation of the rubella virus has continued to be significant with continued occurrence of CRS.

The weakest part of the rubella vaccination strategy, both in the United States and in Europe, has been the vaccination of women of childbearing age [17–20], with some exceptions such as the United Kingdom [21] and Sweden [13]. The reinforcement programme implemented in our hospital through the identification and vaccination of non-immune parturient women was started in 1985 when, despite changes to the childhood vaccination programme, nearly 5% of women admitted to our hospital for delivery continued to be susceptible. In the present study, all parturient women attended in our hospital were included in the vaccination reinforcement programme, and 80% of seronegative women were vaccinated. These figures, together with the fact that 65% of deliveries in the region take place in this hospital, allowed us to assume that at least 50% of all susceptible parturient women in the region were vaccinated.

The percentage of rubella-susceptible parturient women progressively decreased after the beginning of the study and from 1992 was $<1{\cdot}5\%$. The prevalence of rubella-susceptible children and adolescents also decreased and in the mid-1990s was $<5\%$ in all the age groups. The vaccination of infants of both sexes aged 12–15 months and of 11-year-old girls in the 1980s decreased the number of children and adolescents susceptible to rubella and sharply decreased the incidence of rubella infection. However, an immunization gap was created, especially among children born between 1977 and 1982. Many of these children did not receive the first MMR dose, introduced in 1981, either because of their age (born between 1977 and 1979) or because the vaccine coverage was probably low in the years when this vaccine was introduced (born between 1980 and 1982). However, these children grew up in an environment with decreasing viral circulation [9]. Many boys in this cohort remained susceptible after the age of 11 years and formed the basis of the major rubella outbreaks that took place in 1992 and 1996 [22]. The introduction of a second dose of the MMR vaccine in adolescents of both sexes in 1991 reduced the opportunities for viral circulation by including boys among the target population. The coverage maintained with the two-dose MMR vaccination throughout the 1990s as well as that achieved by the catch-up campaign in children aged 5–11 years in 2000 were also high, generally $>90\%$. Sufficient mass immunity was achieved by these strategies to interrupt viral circulation and no indigenous cases of rubella have been confirmed since 1997 nor have any cases (both indigenous and imported) been reported in the last 2 years of the present study.

The prevalence of anti-rubella antibodies in women of childbearing age in distinct regions of Spain has generally been high ($>95\%$) in studies performed since the mid-1980s, and the level of immunity found in the present study is among the highest reported in Spain [8, 19, 23, 24]. The degree of immunity to rubella in women of childbearing age in our environment is similar to that of some northern European countries such as the United Kingdom [21], Finland [14] and Sweden [13], where the prevalence is $>97\%$, and is clearly higher than that observed in other southern European countries such as Italy [14] and Greece [16]. The susceptibility to rubella is also lower than that reported in the United States (11% of women aged between 20 and 49 years during 1988–1994) [17]. During 2001–2002, the prevalence of rubella susceptibility in women was approximately 1–2% in all the age groups, except for adolescent parturient women aged <20 years, in whom it was nearly 5%. This could be partly due to the fact that these adolescents belonged to the cohort born during 1977–1982. In addition, factors such as immigration and other social problems that have been related to a lower level of vaccination [21, 25, 26] should be considered. This observation highlights the importance of offering rubella vaccination to sexually active adolescents, taking advantage of every contact with caregivers [27]. In Spain, until the mid-1980s the incidence of CRS was high [28]. Even though the incidence decreased in subsequent years, sporadic cases were diagnosed until 1999 [29]. In Gipuzkoa, despite an active search using several information sources, we found no cases of CRS that occurred after 1984.

The results obtained in Gipuzkoa demonstrate that vaccination against rubella has been effective in achieving considerable progress towards rubella elimination. To consolidate these results, maintenance of high childhood immunization coverage and low susceptibility to rubella in women of childbearing age as well as an adequate rubella surveillance system will be crucial.

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