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Last cases of rubella and congenital rubella syndrome in Spain, 1997–2016: The success of a vaccination program

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ABSTRACT

With a highly immunized population, rubella infection in Spain is so low that the WHO has declared the elimination of rubella. Rubella in pregnant women is also very rare. The objective of this study is to describe the last cases of congenital rubella syndrome reported and recommend actions to maintain the status of the disease as eliminated.

The CRS cases reported to the Spanish National Epidemiological Surveillance Network between 1997 and 2016 were studied, and the epidemiological, clinical, diagnostic and maternal characteristics of newborns with CRS described. The incidence of CRS was calculated using Birth Statistics from the Spanish National Statistics Agency (INE).

Twenty-three cases of CRS were reported, 70% of which were associated with rubella outbreaks. The most common clinical conditions were heart disease (52.2%), deafness (39.1%) and cataracts (30.4%); 91.3% of cases were confirmed by laboratory testing. 70.0% were born from a non-vaccinated foreign mother, resident in Spain (cumulative rate incidence (CR): 1.1/100,000 births), with mothers coming from Africa (36.0%), Latin America (29.0%), Eastern Europe (21.0%) and Asia (14.0%). Six were born to Spanish mothers (CR: 0.08/ 100,000 births), the last of which were in 2005.

The majority of CRS cases were born to unvaccinated immigrant women infected in Spain during rubella outbreaks. Universal vaccination in childhood is the most efficient strategy to prevent rubella. The limited circulation of the virus will, however, quickly lead to a loss of awareness about rubella among clinicians and epidemiologists. It is necessary to maintain protocols capable of identifying signs consistent with rubella in pregnant women and signs suggestive of congenital rubella in newborns.

1. Introduction

Rubella infection during pregnancy can produce spontaneous miscarriage, death of the foetus or the group of symptoms known as Congenital Rubella Syndrome (CRS), hence the importance of rubella prevention for public health.

Both the level of risk and the kind of defect depend on the gestational age at the moment of infection. If during the first 12 weeks, up to 85% of foetuses will present congenital abnormalities; between the 13th and 16th weeks the risk drops to 10–20%, with malformations becoming rare after the 20th week [1].

Hearing impairment is the most common, and frequently only, symptom of CRS. It can also present itself as eye problems, heart or craniofacial defects, or temporary issues such as purpura, meningoencephalitis, an enlarged liver or spleen, and radiolucent bone diseases in longer bones. Those children who survive infancy may suffer from developmental delays, type 1 diabetes mellitus, or thyroiditis [1,2].

The elimination of a disease is the reduction to zero of the incidence of endemic disease caused by a specific agent in a defined geographical area as a result of deliberate efforts. In 1998 the WHO launched an initiative to eliminate measles in Europe. In 2005 they added the ambition to eliminate rubella and prevent CRS (<1 case per 100,000 living newborns each year) by 2010 [3].

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The region has not succeeded in this objective, and the WHO is evaluating each country on an individual basis, and declaring elimination as appropriate. It is necessary to maintain surveillance and immunization strategies, with necessary immunization rates above 95% using the MMR (Measles, Mumps and Rubella) vaccine in childhood and vaccinating any person susceptible to measles or rubella, irrespective of age [4].

The primary objective of rubella vaccination is to prevent the effects of infection on the foetus. Although 78% of countries vaccinate against rubella, in many places it is still endemic. On a world level, rubella is one of the main infection-related causes of birth defects. The highest risk of CRS is found in countries without rubella vaccination programmes, or with programmes which have only been introduced recently with as yet high levels of susceptibility among women of a fertile age [5,6].

In Spain, the first attempts to prevent the congenital effects of rubella began in 1978, with a programme to immunize girls in schools at 11 years old. Just after, in 1981, the MMR jab was introduced to the infant vaccination schedule; a second dose was added in 1996 [7]. In 2012 the age of first MMR dose administration was brought forward to 12 months (first dose) and 3–4 years old (second dose) [8,9].

In order to monitor the impact of the vaccination programme, rubella was included in the list of diseases that must be officially reported to the Spanish National Epidemiological Surveillance Network (RENAVE) in 1981, and CRS was subsequently added in 1995. It is assumed that there is a CRS underreporting between 1995 and 1999. Achieving high levels of immunization in the general population led to cases of rubella practically disappearing. In 2008, to adapt to epidemiological realities, protocols were updated to improve the sensitivity and the specificity of the surveillance. Some key points for improving surveillance were introduced: the confirmation by laboratory testing of all suspected cases of rubella or CRS, the follow-up of rubella in any pregnant women through to the end of the pregnancy and the active searching for CRS cases in the National Hospitalization Discharge Registry [10,11].

A case which is consistent with CRS presents at least two symptoms from Group A (hearing impairment, congenital heart condition, cataracts, congenital glaucoma or pigmentary retinopathy), or at least one symptom from Group A and one more from Group B (purpura, splenomegaly, microcephaly, delayed development, meningoencephalitis, radiolucent bone disease, or neonatal jaundice which appears within 24 h of birth). A positive laboratory result confirms the case, even if it does not fit the clinical criteria [12,13].

In Spain, vaccinating infants with the MMR jab drastically reduced the incidence of rubella, going from 424 cases per 100,000 in 1983 to 1.32 cases per 100,000 in 1999. The last outbreaks were reported in 2012. Since 2013 endemic transmission has been prevented and only imported cases have been reported. An imported case is when the newborn's mother was in a country in which rubella remains endemic anytime during gestation, and which lacks a link with a rubella case in the home country [12].

The aim of our study is to update CRS epidemiology in Spain by describing the characteristics of the CRS cases, both mothers and children, reported to the RENAVE between 1997 and 2016. Further actions that need to be taken to prevent congenital rubella are discussed.

2. Material and methods

We analysed CRS cases reported to the RENAVE between 1997 and 2016. Additionally, we reviewed the annual reports from the National Measles and Rubella Elimination Programme as well as other relevant national and international publications [14–19]. We also analysed the clinical characteristics of the cases, the moment and place of infection and the laboratory diagnosis. Mothers' origins, vaccination status, their clinical histories of rubella during pregnancy and the results of laboratory tests were studied. The incidence of CRS was calculated using Birth Statistics from the Spanish National Statistics Agency (INE) [20].

3. Results

Between 1997 and 2016, 23 cases of CRS across 10 autonomous communities were reported. In 2000, 2001, 2003, 2006, 2007, 2010, 2015 and 2016 no cases were reported. 13 cases were reported and investigated through the CRS surveillance system and the others were identified retrospectively in the national database of hospital discharges (Table 1). Of the 22 cases of which the sex is known, 14 were male (63.6%). The incidence rate of CRS for 1997–2016 was 0.26 cases per 100,000 births (annual range 0.00–1.29). The majority of the children with CRS were born between September and February.

In 21 cases (91.3%) the clinical presentation is known. Of these, 16 (76.2%) presented at least one symptom from Group A, additionally 16 cases (76.2%) presented at least one from Group B. 14 cases (66.6%) fulfilled the clinical criteria for a CRS case. The most common symptoms were from Group A: congenital heart disease

Table 1
Cases of Congenital Rubella Syndrome by Autonomous Community and reporting year. Spain, 1997–2016.*

	Year											
Autonomous Community	1997	1998	1999	2002	2004	2005	2008	2009	2012	2013	2014	Total
Andalusia					1**		1**				1	**3**
Asturias									2**			**2**
Canary Islands	1**	1**										**2**
Catalonia	1				1	1	1		1			**5**
Castilla-La Mancha						1**				1		**2**
Galicia						1						**1**
Madrid			1	1**,^		2						**4**
Murcia		1**										**1**
The Basque Country								1				**1**
C. Valenciana	1**					1						**2**
Total	**3**	**2**	**1**	**1**	**2**	**6**	**2**	**1**	**3**	**1**	**1**	**23**

Source: National Epidemiology Centre, ISCIII. National Hospitalization Discharge Registry, Ministry of Health.
* Only those years when cases were reported.
** Case recovered from the National Hospitalization Discharge Registry.
^ Case born in Castilla y León but reported in the Autonomous Community of Madrid.

Table 2
Congenital Rubella Syndrome. Clinical manifestations of reported cases in Spain, 1997–2016.

Case identifier		SRC1997/1	SRC1997/2 #	SRC1997/3	SRC1998/1	SRC1998/2 #	SRC1999/1	SRC2002/1 #	SRC2004/1 #	SRC2004/2	SRC2005/1	SRC2005/2	SRC2005/3	SRC2005/4	SRC2005/5 #	SRC2005/6	SRC2008/1	SRC2008/2 #	SRC2009/1	SRC2012/1	SRC2012/2	SRC2012/3	SRC2013/1 #	SRC2014/1	Total
Group A	Hearing impairment				1		1		1					1			1		1	1	1			**9**
	Congenital heart disease					1	1			1	1	1	1			1	1			1	1		1	**12**
	Cataracts						1			1		1				1	1	1					1	**7**
	Glaucoma																							**0**
	Retinitis pigmentosa																							**0**
	Total group A	**0**		**1**	**1**	**3**	**0**	**1**	**2**	**1**	**2**	**1**	**1**	**0**		**1**	**3**	**0**	**3**	**2**	**2**	**2**	**0**	**2**	
Group B	Purpura	1		1							1	1						1						**5**
	Splenomegaly						1				1													**3**
	Microcephaly						1						1			1	1					1		**4**
	Developmental delay		1		1							1				1				1				**5**
	Meningoencephalitis												1											**2**
	Osteopathy											1							1	1				**3**
	Jaundice		1				1	1						1					1			1		**6**
	Total group B		**3**			**2**	**0**	**3**	**1**	**0**	**0**	**2**	**1**	**2**	**1**	**2**	**2**	**0**	**1**	**2**	**0**	**2**	**1**	
Other anomalies						1		1		1		1		1			1					1		**10**
Classification		P	C	C	C	C	C	C	C	C	C	C	C	C	C	P	C	C	C	C	C	C	C	

#Case that does not fulfil the clinical criteria for CRS.
P: Probable CRS case.
C: Confirmed CRS case.
Source: National Epidemiology Centre, ISCIII. National Hospitalization Discharge Registry, Ministry of Health.

(12, 57.1%), impaired hearing (9, 42.8%) and cataracts (7, 33.3%) (Table 2).

Seven cases were considered imported (30.4%) and 16 endemic (69.6%) (Table 3). The endemic CRS cases were associated with epidemics or outbreaks of rubella (Fig. 1).

In 20 cases (86.9%) the age of baby when the diagnosis was established is known. In 15 the diagnosis was made in the first month after birth; three (15.0%) were diagnosed at a month, and two (10%) at two or more months.

21 CRS cases (91.3%) were confirmed by laboratory testing, mostly by IgM serology. For the virological study, in 10 cases samples of urine or nasopharyngeal exudate were collected. Between 1997 and 2007 the viral genotype was characterized in three cases: a 1E genotype in 1998 and two 1J in 2005. Since 2008 in only two cases has the genotype been identified (2B) (Table 4).

3.1. Maternal characteristics

The mean age at the time of giving birth was 26.5 (range 14–40). The vaccination status of 12 mothers is unknown (51.2%); of those that remain (47.8%) only one believed herself to have been vaccinated, although this was without confirming documentation. 14 cases (70.0%) were born to foreign mothers: Morocco and Sub-Saharan Africa (35.7%), Latin America (28.6%), Eastern Europe (21.4%) and Southwest Asia (14.3%) (Table 3). The incidence rate of CRS from 1997 to 2016 was 1.10 per 100,000 births to foreign mothers (range 0.00 to 7.14) and 0.08 per 100,000 Spanish-born mothers (range 0.00–0.51) [Incidence rate ratio = 12.9; CI(95%) = 4.9–33.5; $p < 0.0001$].

A total of 17 mothers (73.9%) suffered a rubella-like disease during pregnancy: 14 (82.3%) during the first trimester, two (11.8%) during the second and one (5.9%) during the third.

Serology was carried out for 10 mothers during their pregnancies. Three had positive IgM results and in another three, seroconversion was identified during pregnancy (Fig. 2).

4. Discussion

The WHO declared Spain free of rubella and congenital rubella in 2015, while in other countries across Europe and the world rubella continues to be endemic. We have presented the cases of congenital rubella from the last 20 years. The results show the impact of the vaccination strategies that have been introduced and the effect of immigration on CRS epidemiology.

Between 1997 and 2016, the objective of elimination was achieved, with < 1 case of CRS per 100,000 live births [3]. The exception was in 2006 when six cases were reported (1.29/100,000 live births), which coincided with a period of high circulation of rubella virus in a number of autonomous communities [15,16,18].

In Spain the combined strategy of selective vaccination of fertile age women and universal vaccination of infants has achieved the elimination of rubella and congenital rubella within 30 years. The vaccination campaigns aimed at adolescents in school contributed substantially to the control of CRS in the birth cohorts that has not as yet benefited from vaccination as infants [7]. The programme was instituted in 1978, and complemented by catch-up campaigns offering the vaccination to all adolescents born from 1964 onwards [21]. Therefore Spain-native women born since 1964 received at least one dose of rubella vaccine while those born since 1986 have received two doses.

As a result of improving coverage with the MMR vaccine -since 1999 national coverage has exceeded 95% for the first dose and 90% for the second dose- immunity against rubella was strengthened. By 1996, 94% of the general population and 96% of women had

Table 3
Congenital Rubella Syndrome. Cases according to mother's birth country. Spain, 1997–2016.*

		Year											
	Country	1997	1998	1999	2002	2004	2005	2008	2009	2012	2013	2014	Total
Europe	Spain		1		1	1 + 1**	2						**6**
	Poland							1					**1**
	Romania									1**	1		**2**
Africa	Ecuatorial Guinea			1**			1						**2**
	Malawi								1**				**1**
	Morocco							1				1**	**2**
America	Colombia						3						**3**
	Dominican Republic									1			**1**
Asia	Philippines	1**											**1**
	Pakistan									1**			**1**
	Unknown	2	1										**3**
Total		**3**	**2**	**1**	**1**	**2**	**6**	**2**	**1**	**3**	**1**	**1**	**23**

Source: National Epidemiology Centre, ISCIII.
* Only those years when cases were reported.
** Imported case.

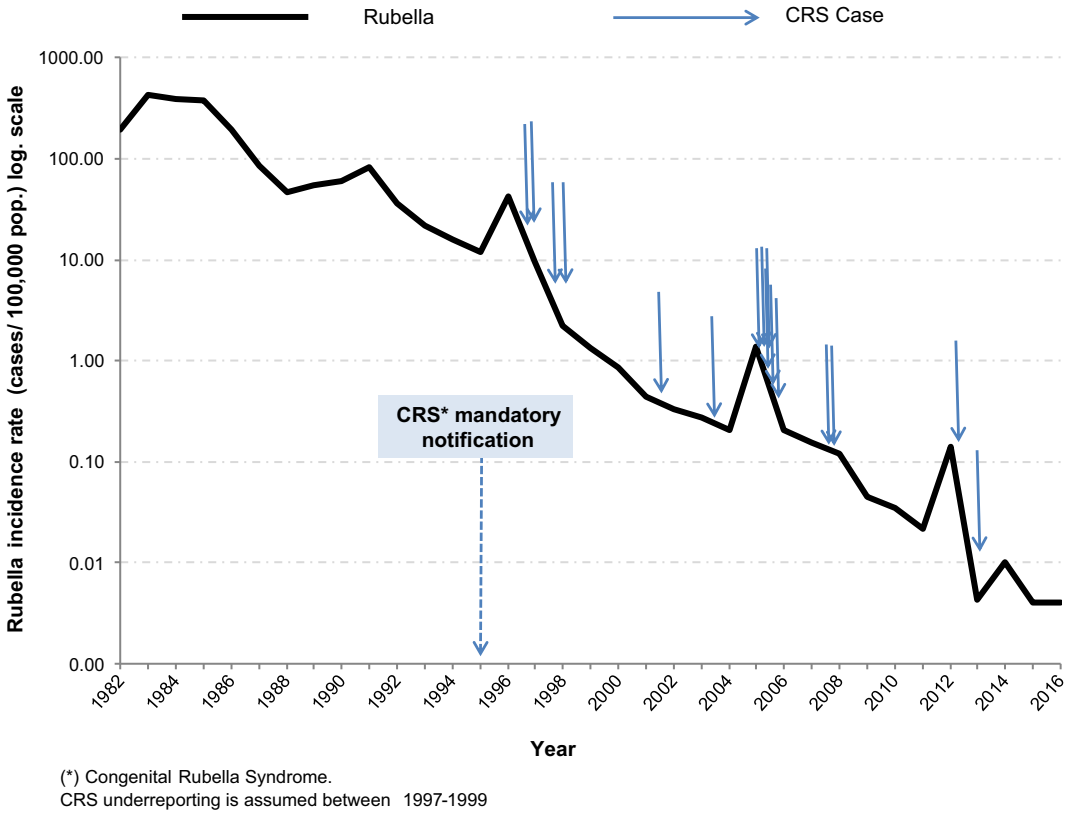

Fig. 1. Incidence of rubella and endemic cases of Congenital Rubella Syndrome by year. Spain, 1982–2016.

antibodies against rubella [18]. Consequently, the epidemiology of rubella moved to an elimination profile, presenting since 1999 a very low incidence and a displacement of the disease towards adults, including women of fertile age [18]. Between 2008 and 2016, 54.4% (99/182) of confirmed cases were found in unvaccinated adults; 28.6% (52/182) had been born outside of Spain, for the most part in Romania [9].

Congenital rubella arises in association, both temporally and geographically, with epidemics and outbreaks of rubella [22]. In our study, the majority of children with CRS were born between September and February, a consequence of the seasonal distribution of rubella cases, which occur during late winter and spring.

The greater part of our cases were classified as endemic as the mothers, both Spanish and foreign, were infected during the course of a rubella outbreak in Spain. Those CRS cases born in 1997–1998 are associated with the epidemic peak that occurred in 1995–1997 [18]; those born in 2004–2005 were a consequence of the outbreaks reported in the Latin-American population of Madrid [14,15], and Barcelona [16]; the CRS cases in 2008 coincided with an outbreak in Algeciras (Andalusia) [17] and other clusters reported in Catalonia, Madrid and the autonomous community of Valencia [9]; those born in 2012–2013 were related to outbreaks which occurred among Romania-origin population residing in Spain, coinciding with a rubella epidemic in Romania between 2011 and 2012 [9,23].

Table 4
Congenital Rubella Syndrome. Clinical samples and results of laboratory tests. Spain, 1997–2016.

CRS identifier	Year of case	Autonomous community	Serum 1			Serum 2			PharyngealExudate	Urine	Genotype
			IgM	IgG	IgGavidity	IgM	IgG	IgGavidity	PCR	PCR	
SRC1997/1	1997	Valencia									
SRC1997/2	1997	Catalonia	Pos	Pos							
SRC1997/3	1997	Canaries	Pos								
SRC1998/1	1998	Murcia	Pos								
SRC1998/2	1998	Canaries	Pos						Pos		1E
SRC1999/1	1999	Madrid	Pos								
SRC2002/1	2002	Madrid	Pos								
SRC2004/1	2004	Catalonia	Pos	Pos	Low				Neg	Neg	
SRC2004/2	2004	Andalusia	Pos								
SRC2005/1	2005	Catalonia	Pos								
SRC2005/2	2005	Madrid	Pos						Pos		1J
SRC2005/3	2005	Madrid	Pos	Pos							
SRC2005/4	2005	Galicia	Pos						Pos		1J
SRC2005/5	2005										
SRC2005/6	2005	Valencia	Pos								
SRC2008/1	2008	Andalusia	Neg				Pos	Low			
SRC2008/2	2008	Catalonia	Pos						Pos	Pos	
SRC2009/1	2009	The Basque Country	Pos								
SRC2012/1	2012	Catalonia	Pos						Pos	Pos	
SRC2012/2	2012	Asturias	Pos						Pos		
SRC2012/3	2012	Asturias							Pos		
SRC2013/1	2013	Castilla-La Mancha	Pos	Pos					Pos	Pos	2B
SRC2014/1	2014	Andalusia	Pos	Pos			Pos		Pos		2B

Source: National Epidemiology Centre, ISCIII.

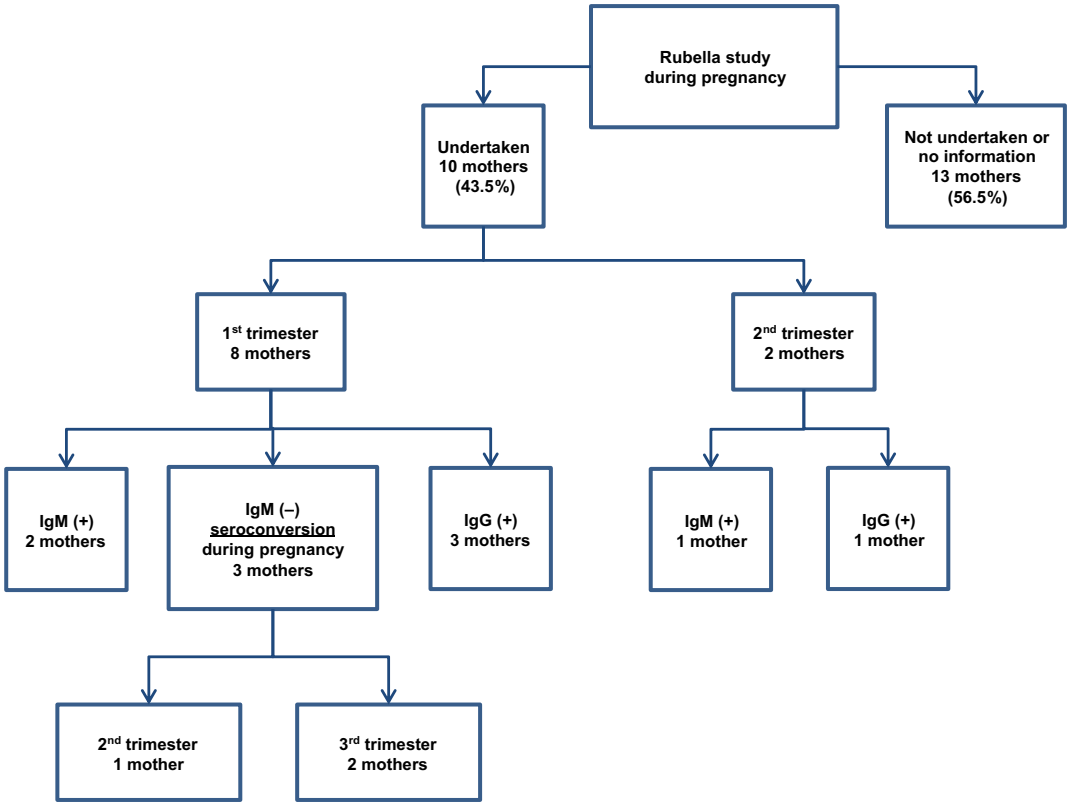

Fig. 2. Congenital Rubella Syndrome. Results of rubella serology carried out on mothers during pregnancy, Spain 1997–2016.

It's worth noting that we cannot discount underreporting of CRS associated to the rubella epidemic occurring in 1995–1997. Although CRS was added to the list of mandatory reporting diseases in 1995, it is well known the lack of awareness about the notification and investigation of suspected disease cases just after launching a surveillance system.

The epidemiology of rubella in Spain correlates with the evolution of immigration into the country. The number of immigrants increased by a factor of 10 between 1997 and 2011 (from 609,813 to 5,751,487). Between 2001 and 2005 the largest influx came from Latin America and afterwards, between 2005 and 2011, immigrants mostly came from Romania.

Immigration from Morocco was constant from 2002 to 2012 but less significant [24].

The geographical concentration of recent arrivals with high susceptibility levels passes above the epidemic threshold and allows outbreaks to develop in the case of an importation. Depending on the degree of grouping of susceptible individuals, an explosive outbreak may result, like that generated in Madrid [15], or smaller outbreaks may be produced, as those which occurred in Aragon in a more dispersed population [9]. This shows the importance of identifying and vaccinating susceptible individuals, above all those who have recently arrived from other countries, international passengers and health-care workers who can produce and spread outbreaks of rubella and other epidemic diseases [25].

The identification of the genotype can help to know the circulation of rubella virus along the time. Genotype 1E was predominant between 1998 and 2003 and was subsequently replaced worldwide by Genotype 2B. The 1J genotype, identified in 2005, is similar to others identified at that time in Brazil [19].

Only six cases from our data set were born to Spanish mothers, the last in 2005. These mothers were more likely to be unprotected because either they had been born before 1986 or they belonged to disadvantaged groups (at least two of the studied mothers belonged to a Roma community). Since 2008 all of the children with CRS were born to unvaccinated non-native mothers, who were infected in pregnancy during a visit to their country of origin or who contracted the disease during an outbreak of rubella in Spain.

Between 2003 and 2008 [23–28] Spanish expectant mothers showed lower levels of susceptibility (2.8–4.6%) than non-natives (7.6–7.7%). These mothers born outside of Spain exceeded the limit of susceptibility to rubella set by the WHO (<5% of fertile age mothers) [3,10] affecting the control of CRS in Spain [11]. Immigration to Spain and its demographic profile have both changed over the last ten years. As a consequence, we need to update the levels of susceptibility to rubella of women in Spain. It is hoped that the second national seroepidemiologic study, conducted in 2017, will provide information relevant for the identification of at risk populations and help orient future actions for the prevention of congenital rubella.

The countries of Africa, the Eastern Mediterranean and Southeast Asia record the highest risk of rubella and congenital rubella. Only the Region of the Americas has been declared rubella-free, confirming at the same time the elimination of CRS [5,6]. In 2016 the Region of Europe shows a heterogeneous situation: 24 countries have already reached the rubella elimination, but despite the introduction of the rubella vaccine across the Region in 2005, endemic transmission was still occurring in 16 countries. Within the EU, Poland (533 cases in 2017), Italy, Germany and Romania continue to report rubella outbreaks and CRS cases [4,6,29].

Continued measures to prevent re-establishment of rubella transmission are required. The most efficient way to preserve rubella and CRS elimination is to maintain high levels of infant vaccination coverage with two MMR doses. Screening for rubella in pregnancy and the post-partum vaccination of susceptible women works as an additional tool to reinforce the immunity of future mothers and prevent congenital rubella [28]. Nonetheless there is controversy regarding the utility of screening in populations where rubella and congenital rubella are rare [30].

In order to document elimination it is necessary to maintain surveillance protocols which permit the identification and confirmation of rubella in pregnant mothers and symptoms suggestive of congenital rubella in newborns [29]. When the circulation of the virus is extremely low, the criteria for clinical suspicion must be very sensitive, in order to facilitate epidemiological and laboratory investigation [10,13]. In our data set a third of the cases showed only one clinical sign; however, they were still reported and laboratory studies were carried out. The effective surveillance of congenital rubella requires the contribution of specialist in epidemiology, paediatrics, gynaecology, cardiology and ophthalmology.

CRS is not a synonym for congenital rubella infection, which also produces miscarriages and late stillbirths. The surveillance of congenital rubella infection is difficult to implement, and it ends up being more useful to monitor CRS by identifying those cases with clinical signs [13].

Since 2003 the RENAVE has been notified of eight cases of rubella during pregnancy, six associated with national outbreaks and two imported infections. In seven cases the pregnancy was ended by abortion and in one case of rubella infection in the third trimester, the pregnancy progressed favourably for both mother and foetus [9].

Most of CRS reported cases were laboratory confirmed, suggesting those CRS that did not investigated in the laboratory could have not been reported and consequently they have been lost. Later identification in national database of hospital discharges improves knowledge of CRS, and at the same time helps identify weaknesses in control and surveillance in hospitals [10,12].

5. Conclusions

During the last 20 years, CRS has been rare in Spain. The majority of cases have been born to unvaccinated non-native mothers. With an extremely low circulation of the virus, we need to know the susceptibility profile of the population in order to identify subpopulations at risk of rubella and congenital rubella.

It is necessary to maintain awareness amongst clinicians and epidemiologists so that signs compatible with rubella can be identified in pregnancy, and signs suggestive of congenital rubella in newborns.

The most efficient measure to prevent rubella is to maintain high vaccination levels with universal vaccination in infancy. Identifying and vaccinating all susceptible individuals, either through specific programmes or by taking advantage of any contact with health services, contributes to the prevention of future cases of rubella and congenital rubella.

Declarations of interest

None.

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CRediT authorship contribution statement

Elina Marjukka Seppälä: Conceptualization, Data curation, Formal analysis, Investigation. **Noemí López-Perea:** Investigation, Software, Supervision, Validation. **María de Viarce Torres de Mier:** Investigation, Validation. **Juan E. Echevarría:** Investigation, Validation. **Aurora Fernández-García:** Investigation, Validation. **Josefa Masa-Calles:** Conceptualization, Investigation, Project administration, Validation.

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