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Shift within age-groups of mumps incidence, hospitalizations and severe complications in a highly vaccinated population. Spain, 1998–2014

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ABSTRACT

The mumps vaccine (Jeryl-Lynn-strain) was introduced in Spain in 1981, and a vaccination policy which included a second dose was added in 1995. From 1992–1999, a Rubini-strain based vaccine was administered in many regions but later withdrawn due to lack of effectiveness. Despite high levels of vaccination coverage, epidemics have continued to appear.

We characterized the three epidemic waves of mumps between 1998 and 2014, identifying major changes in susceptible populations using Poisson regression.

For the period 1998–2003 (P1), the most affected group was from 1 to 4 years old (y) [Incidence Rate (IR) = 71.7 cases/100,000 population]; in the periods 2004–2009 (P2) and 2010–2014 (P3) IR ratio (IRR) increased among 15–24y (P2 = 1.46; P3 = 2.68) and 25–34y (P2 = 2.17; P3 = 4.05).

Hospitalization rate (HR), complication rate (CR) and neurological complication rate (NR) among hospitalized subjects decreased across the epidemics, except for 25–34y which increased: HR ratio (HRR) (P2 = 2.18; P3 = 2.16), CRR (P3 = 2.48), NRR (P3 = 2.41).

In Spain mumps incidence increased, while an overall decrease of hospitalizations and severe complications occurred across the epidemics. Cohorts born during periods of low vaccination coverage and those vaccinated with Rubini-strain were the most affected populations, leading to a shift in mumps cases from children to adolescents and young adults; this also reveals the waning immunity provided by the mumps vaccine. Despite not preventing all mumps cases, the vaccine appears to prevent serious forms of the disease.

1. Introduction

Mumps is a vaccine-preventable disease caused by the mumps virus (MuV, *Paramyxiviridae* family), which commonly appears in childhood in unvaccinated populations or those with low vaccination coverage. The main clinical manifestations of mumps are fever and swelling of the parotid glands. The incubation period for mumps ranges between 15 and 24 days. The main vectors of transmission are salivary droplets, direct contact or contaminated fomites. Complications associated with mumps among children are rare and usually mild; nonetheless, it can lead to complications such as meningitis (1–10% of all infections), encephalitis, orchitis (15–30% of adult men with infection)/oophoritis (5% of adult women with infection) or sensorineural deafness, especially in adults or babies [1–3]. However, up to 30% of mumps cases could be asymptomatic or present with non-specific respiratory symptoms with or without parotitis [2].

Neurological complications due to the MuV may be underestimated, since up to 50% of the meningitis due to MuV comes about without swelling of the parotid gland. A recent study among patients with meningitis or encephalitis without clinical symptoms of parotitis, and in the context of mumps epidemics, detected MuV in cerebrospinal fluid (CSF) in 3.8% of cases (6/158) [4].

Based on data reported to the World Health Organization (WHO), 385,648 cases of mumps were estimated worldwide in 2015 [5]. In Europe, mumps cases have decreased from 243,344 in 2000 to 9939 in 2015 [6], coinciding with high vaccination coverage using Measles Mumps Rubella vaccine (MMR) in most

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European countries [7]. In the Region of the Americas, 43,840 cases of mumps were reported in 2000 and 19,115 cases in 2015 [8]. Despite sustained high vaccination coverages, there is a resurgence in mumps cases and outbreaks of mumps are still occurring [9–14]. This could be explained by low vaccine effectiveness, caused by a waning of vaccine induced immunity [15,16], a decrease in the capacity of the antibodies induced by the vaccine to protect against circulating wild-type MuV, an incomplete cross-reaction between genotypes [17], or antigenic drift [18]. In addition, improvements in diagnostic techniques may also have boosted the reported figures [13,19].

In Spain, the mumps vaccine is delivered as a component of the MMR jab, introduced to the national childhood immunization schedule in 1981 for children aged 15 months. In 1995, a second dose was added at age 11 (y), and it was brought forward to 3–6 years in 1999. In 2012, an update of the national childhood immunization schedule was approved, and set the first dose of MMR at 12 months and the second at 3–4 years [20]. Different vaccine strains have been used as the mumps vaccine antigen. The Jeryl-Lynn strain (JLs) has been administered since MMR vaccine was introduced, but it coexisted with the Urabe strain (1981–1992) and the Rubini strain (1992–1999) in most autonomous regions. The Urabe strain was withdrawn due to adverse effects, and the Rubini strain because of low effectiveness. Since 2000 only the JLs and RIT 4385 strain (obtained from JLs) are administered nationwide [21] (Fig. 1).

In Spain, mumps has been a notifiable disease since 1982. All general practitioners and pediatricians must notify every clinically-suspected case to the National Epidemiological Surveillance Network (Red Nacional de Vigilancia Epidemiológica, RENAVE). In 1996, case-based reporting was implemented with the inclusion of basic epidemiological data (sex, age, case classification, and history of vaccination) and this reporting system became fully functional in 1998. Mumps cases are notified based on the definitions provided by the World Health Organization (WHO) and the European Centre for Disease and Control (ECDC) [21].

A case of mumps is defined as a person with fever and at least one of the following symptoms: sudden onset of swelling, painful to touch parotid or other salivary glands, orchitis. The laboratory criteria to confirm a suspected case should have at least one of these results: specific antibody response to a mumps virus (IgM or IgG seroconversion) in serum or saliva; detection of mumps viral RNA by RT-PCR in saliva, urine or CSF; and/or isolation of mumps virus in saliva, urine or CSF. The epidemiological criterion is defined as contact with a laboratory-confirmed mumps case between 14–25 days before the onset of symptoms [21].

Vaccination coverage in Spain has increased progressively since the introduction of MMR vaccine reaching 80% in 1985. The childhood vaccination schedule against mumps, which provides two separate doses of the MMR vaccine, was consolidated in the 1990s, with high vaccination coverages (>95% for the first dose since 1999 and >90% for the second dose since 2003) [21,22]. Between 1985 and 2012, the mumps incidence rate (IR) decreased about 95%, in line with rates in other industrialized countries [2,23]. Nonetheless, five epidemic waves have occurred despite high vaccination coverage [21] (Fig. 2).

The aim of this study is to find out the reasons for this pattern of outbreaks in a highly-vaccinated population. For this purpose, we characterize the last three epidemic waves of mumps which occurred in Spain between 1998 and 2014, describing incidence rates globally, by age group and by epidemic period, as well as the hospitalization and complication rates, focusing on neurological complications. This will enable us to identify changes in susceptible population throughout the study period and lead to a better understanding the role of the current vaccination programme in providing protection.

2. Material and methods

Data related to mumps cases were obtained from RENAVE.

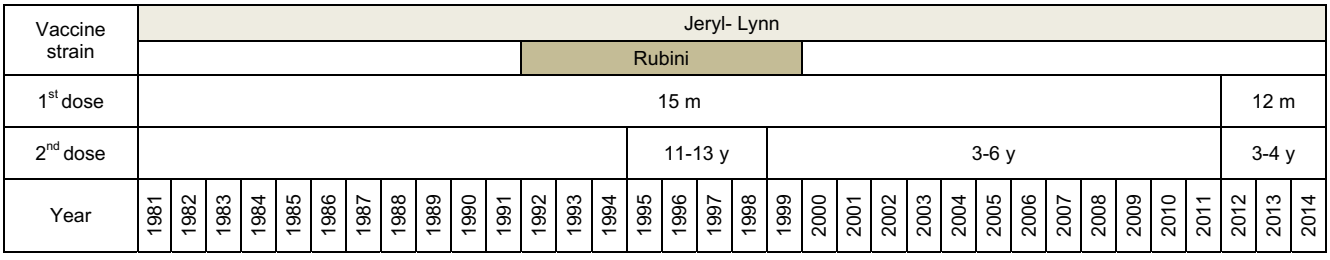
Data for hospitalizations and complications among hospitalized cases were obtained from the National Registry of Hospitalizations Discharge (CMBD) of the Ministry of Health, Social Services and Equality (MofH). Following the Ninth International Classification of Diseases (ICD-9CM) [24] we used these codes, recorded as the principal diagnosis, to analyze complications: 072.2 encephalitis, 072.1 meningitis, 072.0 orchitis, 072.3 pancreatitis, 072.71 hepatitis, 072.79 other complications, 072.8 mumps with unspecified complications, 072.9 mumps without mentioned complication. Data related to national vaccination coverage in Spain was obtained from the MofH [22]. Annual population data for the calculation of rates were obtained from the National Institute for Statistics [25].

We describe the overall mumps incidence rates (IR), the hospitalization rates (HR), complication rates (CR) and neurological complication rates in hospitalized cases (NR) due to mumps in Spain from 1998 to 2014. We have developed the variable "neurological complication" from the codes of meningitis and encephalitis taken together jointly. Data regarding complications are referred to those registered among hospitalized cases.

In order to analyze the evolution of the disease by period and age group, we have defined three periods (P) according to the three different epidemic waves observed between 1998 and 2014: P1 (1998–2003), P2 (2004–2009) and P3 (2010–2014); we also set seven age groups: <1 year, 1–4y, 5–9y, 10–14y, 15–24y, 25–34y and ≥35y.

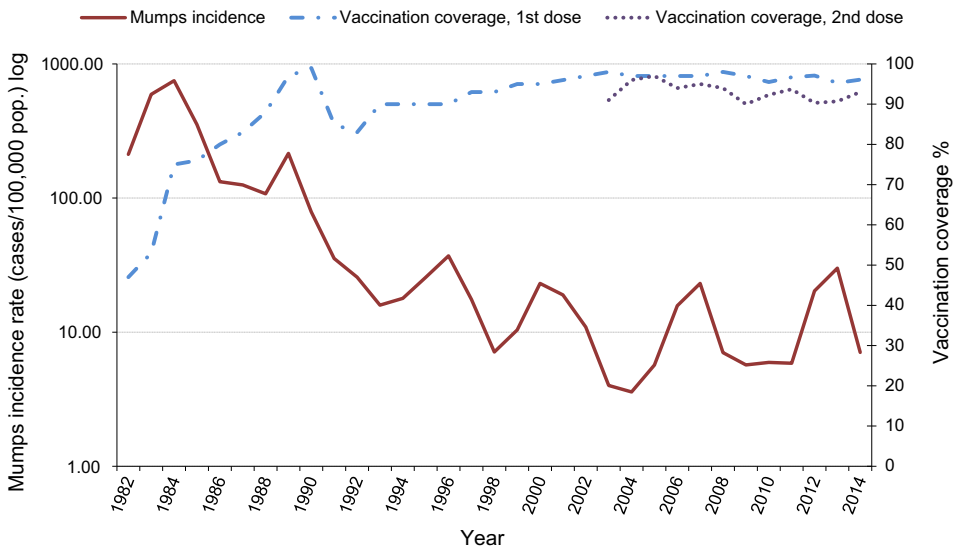
2.1. Statistical analysis

To compare the epidemic waves, period rate ratios for incidence (IRR), hospitalization (HRR), global complications (CRR) and



Source: Ministry of Health, Social Services and Equality

Fig. 1. MMR vaccine: strains of the mumps component and year of introduction of the 1st and 2nd dose. Spain, 1981–2014.



Source: National Epidemiology Centre. ISCIII; Vaccination coverage: Ministry of Health Social Services and Equality

Fig. 2. Mumps incidence rate and vaccination coverage. Spain, 1982–2014.

neurological complications (NRR) were calculated using Poisson regression.

The first period [P1 (1998–2003)] was taken as the reference, then the period rate ratios were expressed as the ratio between the period rates (overall and by age group) and the rate for 1998–2003 in the same group. Statistically significant increases in the rates were considered if IRR, HRR, CRR or NRR > 1 ($p < 0.05$), and statistically significant decreases if IRR, HRR, CRR or NRR < 1 ($p < 0.05$). Confidence intervals (95% CI) were also calculated through Poisson regression, and p-values were defined as statistically significant if <0.05 for both tails. Statistical analyses were performed using Stata© version 14.2 (StataCorp, Texas, USA).

3. Results

In Spain, six epidemics of mumps have occurred between 1982 and 2014, the last three in the context of high vaccination coverage (>95%) (Fig. 2). A total of 1,052,885 cases of mumps were reported to RENAVE between 1982 and 1997, with an overall incidence rate (IR) of 169.5 cases per 100,000 inhabitants. Between 1998 and 2014, 88,598 cases were notified, (global IR = 12.3/100,000 inhabitants (P1 = 12.5/100,000; P2 = 10.2/100,000; P3 = 14.7/100,000).

Related to the study period (1998–2014), the peak for P1 was in 2000 (23.0 cases per 100,000), in 2007 for P2 (23.1/100,000) and in 2013 for P3 (30.0/100,000). The age group 1–4y (IR: 41.1/100,000), followed by 5–9y (IR: 40.1/100,000) had the highest overall rates (Fig. 2).

Different epidemiological patterns regarding the age group were found in each of the three epidemic waves. In P1 the most affected age group was 1–4y (71.7/100,000) followed by 5–9y (64.1/100,000). There was then a shift in P2 and P3, in which the most affected groups were adolescents and young adults [(15–24y): P2, IR = 29.6/100,000; P3, IR = 54.5/100,000] (Table 1 and Fig. 3).

Taking the first wave as a reference, Poisson regression confirms a decrease of mumps incidence among children [(P2) 1–4y: IRR = 0.32; 5–9y: IRR = 0.42. (P3) 1–4y: IRR = 0.45; 5–9y: IRR = 0.45] and an increase in adolescents and young adults in both the second and third epidemic waves. It is especially high among 25–34y: (P2) IRR = 2.17; (P3) IRR = 4.05 (Table 1).

Related to the hospitalizations, a total of 2395 mumps cases were hospitalized (2.6%). The overall rate of mumps hospitalization is 3.2 per million inhabitants. A headline decrease in hospitalizations occurred across the epidemic waves [(P2): HRR = 0.74; (P3): HRR = 0.79].

In the first epidemic wave, hospitalization rates were remarkably high among toddlers [1–4y (P1): 12.8/million inhabitants)] (Table 1 and Fig. 3). The youngest age-groups underwent a significant decrease in hospitalizations across the study period [1–4y: (P2) HRR = 0.47; (P3) HRR = 0.45; 10–14y: (P2) HRR = 0.43; (P3) HRR = 0.58]. Adolescents and young adults experienced a decrease as well [15–24y: (P2) HRR = 0.72] (Figs. 4and 5). The increase over time of hospitalization rates among adults is notable [25–34y (P2): HR = 2.18; (P3) HRR = 2.16] (Table 1 and Figs. 4, 5).

Of hospitalizations due to mumps, 37.3% had associated complications. The global CR was 1.0 mumps hospitalizations with complications/million inhabitants. The 15–24y age group had the highest overall complication rate (3.8/million inhabitants).

The most common complication due to mumps among hospitalized cases was meningitis (n = 364, 15.2%), followed by orchitis (n = 355, 14.8%) and "other complications" (n = 72, 3.0%). Poisson regression confirms an overall decrease in complications for children [5–9y: (P2) CRR = 0.05; (P3) CRR = 0.07; 10–14y: (P2) CRR = 0.15] and an increase for the adolescents and young adult groups [(P3) 15–24y: CRR = 2.03; 25–34y: CRR = 2.48] (Table 1 and Fig. 5).

When it comes to neurological complications, there is a global rate of 0.5 cases per million, with 15–24y the most affected age group (1.8 cases/ million). Overall, there is a decrease of neurological rate ratios across the study period [(P2) NRR = 0.31; (P3) NRR = 0.35]. Nonetheless, there is a significant increase in P3 for 25–34y (NRR = 2.41) (Table 1).

4. Discussion

In Spain, after the introduction of the MMR vaccine in 1981, mumps rate dropped dramatically. However, since 1998 an overall decrease in the incidence of mumps is not observed and despite the achievement of high vaccination coverage, the disease continues to have a cyclic presentation. This study contributes to better understanding of what is going on the epidemiology of mumps in highly vaccinated populations.

We showed different epidemiological patterns across the three epidemic waves. The occurrence of periodical outbreaks is in line

Table 1
Mumps incidence rates, incidence rate ratios; mumps hospitalization rates, mumps hospitalization rate ratios; complication rates, complication rate ratios; neurological complication rates and neurological complication rates ratios, by period and age group. Spain. 1998–2014.

Age group (years)	Mumps incidence rates[a]			Incidence rate ratios[b] (IRR)		Mumps hospitalization rates[a]			Hospitalization rate ratios[b] (HRR)		Mumps complication rates[a]			Complication rate ratios[b] (CRR)		Neurological complication rates[a]			Neurological complication rate ratios[b] (NRR)	
	1998–2003	2004–2009	2010–2014	2004–2009 (CI 95%)	2010–2014 (CI 95%)	1998–2003	2004–2009	2010–2014	2004–2009 (CI 95%)	2010–2014 (CI 95%)	1998–2003	2004–2009	2010–2014	2004–2009 (CI 95%)	2010–2014 (CI 95%)	1998–2003	2004–2009	2010–2014	2004–2009 (CI 95%)	2010–2014 (CI 95%)
<1 year	44.3	11.6	5.8	0.26 (0.23–0.29)	0.13 (0.11–0.16)	9.7	8.5	7.8	0.87 (0.49–1.54)	0.81 (0.44–1.50)	1.3	1.1	0.0	0.83 (0.11–5.93)	–	2.9	0.0	0.0	Insufficient observations	Insufficient observations
1–4 y	71.8	23.1	32.7	0.32 (0.31–0.34)	0.45 (0.44–0.48)	12.8	6.0	5.7	0.47 (0.35–0.64)	0.45 (0.33–0.62)	4.6	0.6	0.5	0.49 (0.18–1.37)	0.34 (0.09–1.26)	5.8	0.8	0.3	0.43 (0.01–0.18)	0.02 (0.00–0.18)
5–9 y	64.1	27.4	29.6	0.42 (0.41–0.45)	0.46 (0.44–0.48)	10.4	2.4	2.6	0.23 (0.15–0.34)	0.25 (0.17–0.37)	5.2	0.1	0.2	0.05 (0.01–0.42)	0.07 (0.01–0.55)	7.3	0.0	0.3	Insufficient observations	0.02 (0.00–0.13)
10–14 y	30.5	31.6	28.5	1.03 (0.99–1.08)	0.93 (0.89–0.98)	5.6	2.4	3.3	0.43 (0.28–0.65)	0.58 (0.39–0.86)	2.5	0.2	0.9	0.15 (0.03–0.67)	0.66 (0.25–1.72)	5.6	0.3	1.3	0.05 (0.01–0.35)	0.21 (0.07–0.62)
15–24 y	20.3	29.6	54.5	1.46 (1.41–1.50)	2.68 (2.60–2.76)	6.9	5.0	5.7	0.72 (0.58–0.88)	0.90 (0.73–1.11)	4.9	3.2	3.0	0.93 (0.58–1.49)	2.03 (1.31–3.17)	12.3	4.6	2.4	0.54 (0.38–0.79)	0.52 (0.34–0.78)
25–34 y	4.6	9.9	18.5	2.17 (2.06–2.30)	4.05 (3.84–4.26)	1.4	3.1	3.1	2.18 (1.60–2.97)	2.16 (1.56–2.99)	0.7	1.7	1.6	1.25 (0.64–2.43)	2.48 (1.30–4.70)	8.1	5.6	4.9	1.49 (0.79–2.83)	2.41 (1.30–4.49)
≥35 y	1.6	2.2	3.7	1.41 (1.33–1.49)	2.34 (2.22–2.47)	2.3	2.4	1.9	1.06 (0.91–1.23)	0.87 (0.74–1.02)	0.2	0.2	0.2	0.80 (0.47–1.36)	0.61 (0.33–1.14)	5.4	2.7	2.2	0.71 (0.29–1.71)	0.94 (0.40–2.17)
Total	12.5	10.2	14.7	0.81 (0.80–0.83)	1.17 (1.15–1.19)	3.9	3.0	2.8	0.74 (0.67–0.82)	0.79 (0.72–0.87)	1.5	0.8	0.4	0.65 (0.50–0.86)	0.96 (0.73–1.25)	1.0	0.3	0.3	0.31 (0.24–0.40)	0.35 (0.27–0.45)

[a] Cases per 100.000 population. Hospitalizations, overall complications and neurological complications due to mumps per million population.
[b] Poisson Regression (reference period 1998–2003). 95% Confidence Interval.

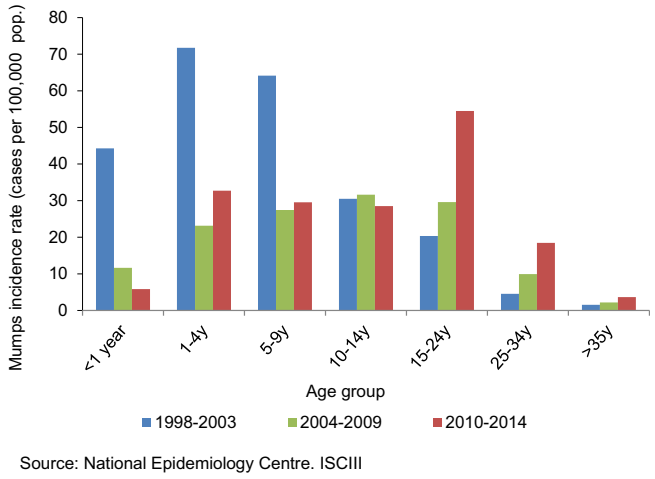


Fig. 3. Mumps incidence rates by epidemic period and age group. Spain, 1998–2014.

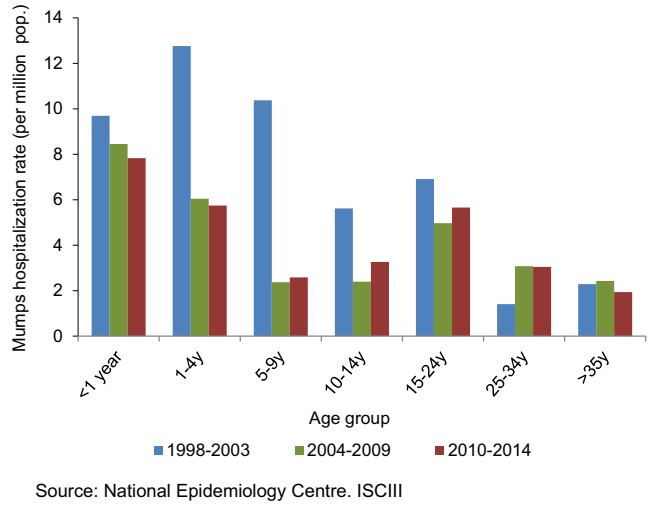


Fig. 4. Mumps hospitalization rate, by epidemic period and age group. Spain, 1998–2014.

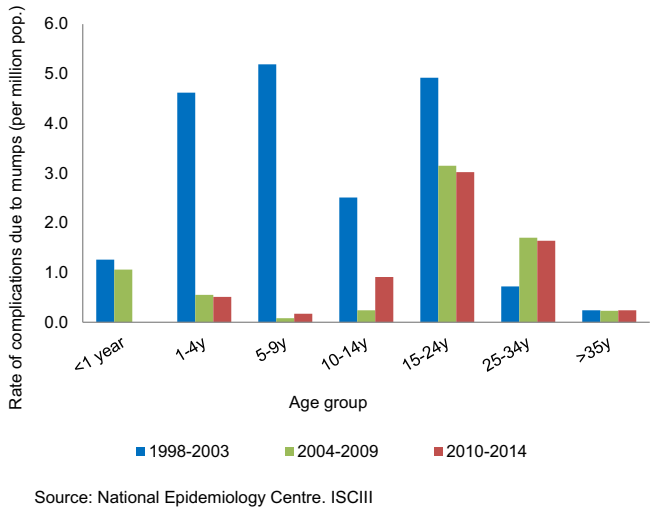


Fig. 5. Rate of complication due to mumps among hospitalized cases, by epidemic period and age group. Spain, 1998–2014.

with other countries which have a similar context of high vaccination coverage [9,26–29]. During the first epidemic wave, children between 1 and 14 years had the highest mumps incidence rates; these children coincided with the use of the Rubini strain, low vaccination coverages and/or with the earliest years after the introduction of the MMR vaccine [30,31]. The low incidence among adults may be attributable to their high levels of exposure to the wild mumps virus in their childhood, so they were able to develop natural immunity, as has been suggested by other studies [32]. The presentation of mumps in this wave is similar to the behaviour of mumps in the prevaccination era. In the second and third waves, adolescents and young adults were the most affected age groups (those who were children and toddlers in the first wave). The key feature that could explain the number of outbreaks notified in these cohorts is that they were most likely vaccinated with at least one dose of Rubini strain (between 1992 and 1999) [10,30,33–39] which has demonstrated low effectiveness, and which finally led to its withdrawal [32,40,41]. A seroepidemiological study conducted in 1996 in Spain revealed a low vaccine-effectiveness for mumps (76.7–79.3% depending on the age). This finding was mainly associated with the Rubini strain, showing a prevalence of mumps antibodies in children of 65.5%, significantly lower than the prevalence in those vaccinated with the JL strain (86.0%) [40]. Another factor, not analyzed in our study, is the change in the mumps genotype in circulation across the epidemic waves: during the first one, genotype H was predominant in Spain, while in the second and third waves it was replaced by genotype G [42].

Regarding the limited effectiveness of the mumps vaccine, cases among individuals vaccinated with two doses of JLs are not rare in populations with high vaccination-coverages [27,37]. In our study this issue was not evaluated at an individual level, but we assume that, nationwide, cohorts born from 1999 onwards have received both doses of JLs [21,22] in a context of high vaccination-coverage. Reported cases among these well-vaccinated cohorts with two JLs doses may be explained by the waning immunity provided by the mumps vaccine, as has been described in other studies [9,15,16,29,43–45], some of them in Spain [43,46]. The waning protection of the vaccine can be evaluated accurately in those cohorts born after 1999, in the subsequent epidemic waves.

Crowded places with many young people, like high-schools or universities, are likely the sites for mumps outbreaks. Among adolescents and young adults a particular contact pattern is described, with a higher number of close contacts than adults or children. The gathering of susceptible people among this age group is common, and associated with the waning immunity of the mumps vaccine, leads to an increase in the risk of infection [9,11,16,29,45,47,48]. In Spain, several outbreaks have been described along these lines [10,35,37,49], especially in the third wave, when the rate among young people between 15 and 24y exploded. Catch-up campaigns administering a third dose of MMR vaccine (JL strain) to susceptible cohorts were carried out for outbreak control across the study period [34,35]. This is a control measure described in other countries with high vaccination-coverages [12,50].

Regarding hospitalizations due to mumps, a shift from toddlers to adolescents and young adults across the epidemic waves has occurred. Our results show an overall relative lack of complications due to mumps in the post-vaccine period. Major rates of hospitalizations and complications associated with mumps, among adolescents and young adults (15–24 years) are also found in other studies [9,26,27,32]. In spite of the fact that there was not an overall decrease in mumps incidence, hospitalization rates have experienced a global decline; this supports the notion that, despite the MMR vaccination not preventing every mumps case, it represents an effective measure for reducing the risk of severe forms of the disease [15,27,44,48,50].

Neurological complications due to mumps are rare, but may be severe enough to be warrant action to prevent them. In England and Wales, before the introduction of the MMR vaccination, mumps was the main cause of viral meningitis [51]; it almost disappeared since the vaccine's introduction. Other studies in Spain have shown that, before widespread use of the MMR vaccine, infection with the mumps virus was a major cause of aseptic meningitis, particularly in children [52]. Our study shows an overall decrease in neurological complications across the last three epidemic waves in Spain. The great decrease in these complications supports the usefulness of the vaccine to prevent severe cases. Nevertheless, the resurgence of mumps among adults, who are especially susceptible to suffering severe complications, may reduce the effectiveness of the vaccine in this sense.

The main complication registered in this study in hospitalized mumps cases was meningitis, in contrast with other studies which showed orchitis as the most prevalent complication [2,26,27,44,48,51]. Our source for mumps hospitalization data is the National Registry of Hospitalization Discharges (CMBD); this could explain the different distribution of complications compared to other studies, as it would be expected that severe cases are the most likely to be hospitalized. Orchitis can have different clinical presentations, ranging from mild to severe forms; as a consequence many cases might not be hospitalized.

5. Conclusions

In Spain despite a context of high vaccination coverage, mumps continues to appear in a cyclic presentation. During the last 15 years, mumps has changed from being a childhood disease to an illness affecting adolescents and young adults. This is consistent with the history of vaccination with MMR in the country, where the most affected cohorts were either unvaccinated, born in years with low coverage levels, had a single dose (Rubini/Jeryl-Lynn) or had two doses, but one of them was the Rubini strain. Moreover, those who were well-vaccinated with two doses of JLs based vaccine may still get the disease.

Nevertheless, overall, hospitalizations and severe associated complications were reduced significantly after the introduction of the MMR vaccine. The current antigen component of mumps in the MMR vaccine is not effective enough to eliminate the disease, but it is crucial to the reduction in hospitalizations and severe associated complications, such as meningitis. Maintaining a high vaccination-coverage with two doses might represent the key in preventing severe complications.

We recommend maintaining high vaccination coverages with MMR and if an outbreak occurs, to consider the vaccination of susceptible cohorts.

Author contribution

Noemí López-Perea: design for the study, data analysis, writing as main author. Josefa Masa-Calles drafted and revised the manuscript. Aurora Fernandez-García, María de Viarce Torres de Mier, Juan E. Echevarría and Fernando de Ory reviewed and assisted in the editing of the final version of the manuscript. María Victoria Martínez de Aragón: mentoring and revised drafts and the final version.

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Conflict of interest

The authors declare that they have no conflict of interest.

Notes

For this type of study formal consent is not required.

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