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Effectiveness of Jeryl Lynn-containing vaccine in Spanish children

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ABSTRACT

We evaluated the effectiveness of the Jeryl Lynn strain vaccine in a large outbreak of mumps in Navarre, Spain, 2006–2008. Each of the 241 cases of mumps occurring in children over 15 months of age born between 1998 and 2005 was compared with 5 controls individually matched by sex, birth date, district of residence and paediatrician. Vaccination history was obtained blindly from clinical records. Conditional logistic regression was used to obtain the matched odds ratios (ORs), and effectiveness was calculated as 1 − OR. Some 70% of cases had received one dose of measles–mumps–rubella vaccine, and 24% had received two doses. Overall vaccine effectiveness was 72% (95% CI, 39–87%). Two doses were more effective (83%; 54–94%) than a single dose (66%; 25–85%). Among vaccinated children, risk was higher in those who had received the first dose after 36 months of age (OR = 3.1; 1.2–8.4) and those who had received the second dose 3 or more years before study enrolment (OR = 10.2; 1.5–70.7). Early waning of immunity in children after the second dose may contribute to reduced vaccine effectiveness for mumps prevention.

1. Introduction

The existence of an effective vaccine against mumps has led some countries to propose the objective of eliminating or controlling this disease [1,2]. Initially, mumps outbreaks were related with failures in vaccination coverage [3]. However, some areas with high coverage with two doses of trivalent measles–mumps–rubella (MMR) vaccine have also experienced mumps outbreaks affecting both vaccinated and unvaccinated children and young adults [4–6].

In evaluations of mumps vaccine in outbreak settings, the mean effectiveness has been estimated as 77% (range 61–91%), lower than the efficacy estimated in experimental studies [7]. Waning immunity could be one reason for this limited effectiveness, and may explain the emergence of mumps outbreaks in older vaccinated populations [8–10].

Mumps outbreaks have occurred in various regions of Spain between 2006 and 2008, affecting a substantial number of vaccinated persons, with predominance of the G1 genotype [11,12]. In the region of Navarre, with over 95% vaccination coverage in the population born since 1980 and hardly any mumps virus in circulation since 1993, a widespread outbreak resulting in some 3000 cases of mumps occurred between August 2006 and June 2008. In the context of this population-based outbreak, we evaluated the effectiveness of the vaccine containing the Jeryl Lynn strain in preventing mumps cases in children and investigated the possible existence of waning immunity.

2. Materials and methods

2.1. Study setting

This study used various sources of health information covering a population of some 600,000 persons in Navarre. The trivalent MMR vaccine is included in the childhood immunization schedule and has been covered by public financing since 1982. The schedule calls for one dose of vaccine at 15 months of age and a second dose, which was initially given at 11 years of age and was subsequently moved up to 6 years of age in 1999 and to 3 years of age in 2007, with the objective of eliminating measles. In the cohorts born since 1998, only MMR vaccine containing the Jeryl Lynn strain has been used. The vaccine doses given are recorded on the child's vaccination card, in the primary care clinical record, and in the regional vaccination registry.

Mumps is a notifiable disease in Navarre, and both clinically suspected and laboratory-confirmed cases are routinely reported through a computerized information system to regional health authorities. Cases are considered clinically compatible if there is

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Table 1
Characteristics of mumps cases according to measles–mumps–rubella vaccination status.

	Non-vaccinated *N* (%)	One dose *N* (%)	Two doses *N* (%)	Total *N*
Sex				
Male	10 (9)	79 (68)	27 (23)	116
Female	3 (2)	90 (72)	32 (26)	125
Age, years				
1–3	5 (8)	54 (90)	1 (2)	60
4–6	6 (5)	109 (85)	13 (10)	128
7–10	2 (4)	6 (11)	45 (85)	53
Residence in the capital city	8 (5)	112 (74)	32 (21)	152
Viral isolate by culture	1 (11)	8 (89)	0	9
Serology result				
IgM+	2 (20)	6 (60)	2 (20)	10
IgM−/IgG+	0 (0)	21 (66)	12 (34)	33
Total	13 (5)	169 (70)	59 (24)	241

swelling of one or more salivary glands lasting at least 2 days. Confirmation is made by virus isolation, by detection of RNA by polymerase chain reaction (PCR), or by elevated specific IgM. Cases epidemiologically linked with another clinical case of mumps are also considered confirmed [13].

Between August 2006 and June 2008 an extensive outbreak of mumps occurred in Navarre, with some 3000 cases and an attack rate of 1% of the population under 30 years of age. The highest incidence was reported in young adults aged 19 years, although cases occurred in all ages. About 14% of the cases were confirmed by laboratory. The seven strains processed in the National Reference Laboratory belonged to genotype G1. The highest incidence was registered in adolescent cohorts vaccinated with the Rubini strain, but incidences were also high in the cohort vaccinated with the Jeryl Lynn strain [14].

2.2. Information sources and study design

To assess the effectiveness of this vaccine, we designed an individually matched case–control study. The cases were all children residing in Navarre born between 1998 and 2005 who had a diagnosis of mumps confirmed microbiologically or epidemiologically between August 2006 and June 2008. Cases occurring before age 15 months were excluded, as were those whose paediatrician could not be identified. For each case, 5 individually matched controls were selected among children with the same sex, municipality, district of residence and paediatrician. Matching was performed by selecting controls with the closest birth date within the same calendar semester to the corresponding case. We excluded as controls those children who had been diagnosed with mumps before the date the case was diagnosed or who had not fulfilled all the pairing criteria since the beginning of 2006; these children were replaced with the next child who met the inclusion criteria.

2.3. Vaccine status assessment

The number of doses and dates of vaccination of cases and controls were ascertained in a blinded review of the primary care vaccination registry. In the event that an age-appropriate vaccination was missing without documentation of the reason, the parents were contacted by phone to confirm this information and check it against the vaccination card. For both cases and controls, vaccination with strains other than Jeryl Lynn was ruled out. Some children with severe allergy to eggs had received the vaccine obtained in cell cultures that included measles and rubella, but not mumps (Moruviraten™), therefore these doses were not considered for the purpose of mumps vaccination. We considered only doses administered up to 30 days before the date of symptom onset in the corresponding case.

The Ethics Committee of the Health Department of Navarre approved the protocol of this study.

2.4. Statistical analysis

We first compared all cases with their respective controls to estimate the effectiveness of one or two doses of vaccine in preventing mumps. Vaccinated cases were compared with their respective controls who had also been vaccinated to evaluate the effect of the second dose and the effect of the time of administration of the first dose in preventing mumps. Finally, cases who had received two doses of vaccine were compared with their respective controls who had also been vaccinated with two doses to determine the influence of the time since application of the last vaccine dose on the risk of disease.

Unmatched dichotomous variables were compared by χ^2 or Fisher's exact tests, and continuous variables by Wilcoxon's test. Matched odds ratios (ORs) for vaccination, with their 95% confidence intervals (CIs), were calculated with conditional logistic regression. Vaccine effectiveness was calculated as 1 minus the matched odds ratio. We set the level of significance as two-sided $P < 0.05$.

3. Results

3.1. Characteristics of cases and controls

Of the 251 cases of mumps confirmed in children born since 1998, we excluded 6 who had not reached 15 months of age and 4 whose paediatrician in Navarre could not be identified. Of the 241 cases analysed, 48% were males and 63% resided in the capital city. The median age of cases at time of diagnosis was 64 months, ranging from 16 to 124 months. Some 5.4% (13 cases) were not vaccinated, 70.1% (169 cases) had received one dose of MMR vaccine, and 24.5% (59 cases) had received two doses. The vaccinated children had received the first dose between 11 and 72 months of age, with a median of 15 months, and the second dose between 37 and 88 months of age, with a median of 77 months.

Table 2
Estimates of effectiveness of the MMR vaccine for mumps prevention. Conditional logistic regression analysis.

	Cases/controls	Vaccine effectiveness (%)	95% confidence interval	*P*-value
Model 1				
Non-vaccinated	13/23			
Vaccinated	228/1182	72	39–87	0.0013
Model 2				
Non-vaccinated	13/23			
1 dose	169/852	66	25–85	0.0075
2 doses	59/330	83	54–94	0.0005

Table 3
Effect of number of doses and age at first dose on risk of mumps among children vaccinated with any dose of measles–mumps–rubella vaccine. Multivariate conditional logistic regression analysis.

	Cases/controls	Matched odds ratio	95% confidence interval	*P*-value
Doses of vaccine				
1	169/809	1		
2	59/314	0.51	0.20–1.27	0.1463
Age at first dose, in months				
<14	9/25	1.98	0.91–4.29	0.0845
14–35	212/1087	1		
≥36	7/11	3.11	1.15–8.43	0.0254

Nine cases were confirmed by virus isolation, another 10 by positive IgM, 7 by epidemiologic relation with another laboratory-confirmed case, and all the rest, by epidemiologic relation with other cases with a clinical diagnosis of mumps (Table 1). Thirty-three cases had positive IgG and negative IgM, although this was not considered a confirmation criterion. About 84% of the laboratory-confirmed cases were vaccinated and 11% had received two doses.

Among the controls, 98.1% were vaccinated, and 95.7% of those older than 6 years had received two doses of MMR vaccine.

The unmatched comparison of cases and controls showed a higher percentage of non-vaccinated persons in the first group (5.4% vs. 1.9%, $P = 0.005$). The median age in vaccinated cases was 15 months (range 11–72) at the first dose and 77 months (range 37–88) at the second dose. Vaccinated cases and controls did not differ in the age at which they received each dose.

3.2. Effectiveness of the vaccine

Table 2 shows the results of the conditional logistic regression analysis. The effectiveness of having received any dose of MMR vaccine was 72% (95% CI, 39–87%). The effectiveness of two doses of vaccine reached 83% (95% CI, 54–94%), and that of one dose was 66% (95% CI, 25–85%).

The analysis limited only to those children who had received any dose of MMR vaccine showed that the second dose provided a non-statistically significant additional protection of 49% compared to those who had only one dose. Administration of the first dose before 14 months or after 36 months of age was associated with a higher risk of mumps compared to those who had been vaccinated within this age interval, although the risk reached statistical significance only in the latter age group (OR = 1.98; 95% CI 0.91–4.29 and OR = 3.11; 95% CI 1.15–8.43, respectively) (Table 3). In 57% of cases and 56% of controls who received the first dose after 36 months of age the MMR vaccine had been co-administered with other vaccines.

The analysis limited only to children vaccinated with two doses showed that the risk of mumps was higher with increasing time since the last dose of MMR vaccine (Table 4). Those who had received the second dose 3 or more years before study enrolment had a higher risk of mumps than those who had received the second dose within the last 3 years (OR = 10.19; 95% CI 1.47–70.73). Another well-adjusted model was obtained using the square of time since the second dose, in years, as a continuous variable (OR per square year 1.22; 95% CI 1.02–1.46).

4. Discussion

In children age 1–10 years we found the MMR vaccine containing the Jeryl Lynn strain to be 72% effective in preventing cases of mumps. The effectiveness was 66% for one dose and reached 83% after the second dose. These results are similar to the ranges of effectiveness found in previous studies conducted in outbreak settings [8–10,14–16], although some of these studies analysed adolescents and young adults for whom the time since vaccination was much longer. Since the birth of the study children, there had been scarcely any mumps virus in circulation in Navarre, therefore previous natural immunity or the booster of the vaccine effect by asymptomatic infections was highly unlikely. Between August 2006 and July 2008 the virus came into general circulation, as shown by the fact that 1% of the population under age 30 was affected despite high vaccination coverage. It can thus be affirmed that a large portion of the population, including the controls, would probably also have been exposed to the infection during this outbreak.

Possible explanations for the moderate effectiveness of the vaccine are primary vaccine failure, loss of secondary effectiveness, and infection by heterologous viruses [17–20].

Primary vaccine failure could be due to problems with vaccine conservation and to failure of the immune response. However, following the guidelines for maintaining and managing the vaccine cold chain, when any relevant problem was detected all affected doses were discarded [21]. Furthermore, we did not find mumps cases to be especially concentrated in children vaccinated with a particular batch, nor in those vaccinated at the same time and place. The lower response in vaccinated children as a function of age, especially before 12 months, has been described [17]. We found that administration of the first dose of MMR vaccine after the third year of life was associated with lower protection. These late vaccinations sometimes occur when missed vaccinations are brought up to date, a situation in which the MMR vaccine is frequently co-administered with other vaccines. However, our results do not permit any conclusion about the relation between simultaneous vaccination and loss of effectiveness.

Table 4
Effect of the time of administration of each dose on the risk of mumps among children vaccinated with two doses of measles–mumps–rubella vaccine. Multivariate conditional logistic regression analysis.

	Cases/controls	Matched odds ratio	95% confidence interval	*P*-value
Age at first dose, in months				
<14	3/9	1.89	0.47–7.64	0.3710
14–35	54/262	1		
≥36	2/3	3.88	0.63–24.01	0.1452
Time since second dose, in months				
<24	42/206	1		
24–35	13/61	2.00	0.55–7.24	0.2934
≥36	4/7	10.19	1.47–70.73	0.0189

Consistent with other studies, we found that vaccine effectiveness was lower with increasing time since the last dose, which has been explained by waning immunity [9,10,18]. One study of mumps vaccine immunogenicity showed that a second dose of vaccine 4–5 years after the first dose at age 14–18 months increased seropositivity rates from 86% to 95%, but 9 years after the first vaccination, the seropositivity rate had returned to 86% [19]. In another study, 19% of children who had received one dose of vaccine had no detectable antibodies 4 years after vaccination [20]. Our results indicate that this effect of waning immunity begins early, as seen in the fact that 3 or more years after the second dose of MMR vaccine, the risk of mumps was 10 times higher. This increased risk does not appear to be linear, but rather is accentuated over time. This effect may have favoured the absence of a booster effect given the lack of circulating mumps virus during the lifetimes of these children. In view of these results, moving the second MMR dose to 3 years of age, a strategy designed to strengthen measles elimination, could be detrimental for mumps control given that there is no plan for a subsequent booster dose and there are no natural booster infections.

Infection by heterologous viruses facilitated by a genotype-specific neutralising antibody response could be a cause of lower effectiveness [22]. Thus, mumps vaccine induced immunity (derived from genotype A virus) may be less effective against genotype G, which was the cause of this outbreak [14]. However, the vaccine effectiveness we found in an outbreak due to genotype G does not appear to differ substantially from that described in outbreaks caused by other genotypes, although our evaluation included children younger than those in most of the other studies [7].

The estimate of vaccine effectiveness in this observational study may be subject to some limitations. Problems of comparability between the vaccinated and unvaccinated groups could bias the estimate of vaccine effectiveness downward when evaluating it in the context of an outbreak [23]. The selection of controls, paired by sex, year of birth, municipality, district of residence and paediatrician, provides good comparability with the cases with regard to opportunities for vaccination, registering of the doses administered, probabilities of exposure to the virus, and access to disease diagnosis. Unlike other outbreaks confined to a single study centre or residence, the controls may have had less exposure to infection than the cases in this population-based outbreak. This would not be a problem, however, so long as they accurately reflect vaccination status in the population from which the cases were taken [24].

We included only clinical cases confirmed by laboratory or by a defined epidemiologic criterion [13], which makes classification bias with regard to diagnosis unlikely. Vaccination histories were obtained blindly from documented clinical sources. When mumps vaccination was not documented in these sources, we checked to confirm that it had not been received and to determine the reason why not; lack of data was not assumed to be equivalent to non-vaccination. Vaccination coverage in both cases and controls was very high in accordance with the recommended schedule, which makes it unlikely that vaccine status was underestimated.

5. Conclusions

This study adds to the literature showing moderate effectiveness of the mumps vaccine containing the Jeryl Lynn strain, which seems to be related with early and progressive waning immunity. This effect, seen in children vaccinated with both one and two doses, makes it difficult to control the disease even when high vaccination coverage is achieved, and leaves open the possibility that outbreaks will occur when the infection is reintroduced. Possible solutions to attain higher and more lasting levels of protection include the development of new vaccines, adding a third dose of MMR vaccine [25] and exploring modifications to childhood immunization schedules to optimise the performance of the current vaccine for mumps control [26].

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