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MMR vaccine effectiveness in an outbreak that involved day-care and primary schools

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ABSTRACT

Objective: In 2006, a large measles outbreak occurred in Catalonia (Spain), where the immunization schedule included two doses of MMR vaccine at 15 months and 4 years. The aim of this study was to investigate the vaccine effectiveness (VE) of MMR in children attending day-care and pre-school centres and to estimate the number of cases that would have been avoided by administering the first dose of MMR at 12 months.
Methods: A retrospective cohort study was carried out between October 2006 and January 2007 in day-care and pre-school centres with confirmed measles cases. VE was calculated in children aged ≥15 months without previous measles infection. Cases avoided by advancing the first dose of MMR to 12 months were estimated by calculating the basic and effective reproduction number in centres where transmission outside the class was observed.
Results: Fifteen centres and 1394 children were included. There were 77 confirmed cases (attack rate = 5.5%). Vaccination coverage of the 1121 children aged ≥15 months was 91.6% and VE was 96% (95%CI 89–98%).

There were 33 (41%) cases in the 81 children aged 12–14 months. Advancing the first dose to 12 months would have prevented 74 cases (91.5%) and lowered the attack rate from 41% to 8.6%.
Conclusions: Over 90% of cases in children aged 12–14 months would have been avoided by MMR administration at 12 rather than 15 months. We strongly recommend advancing the first dose of MMR to 12 months in order to reduce the risk of measles outbreaks.

1. Introduction

Measles, a disease caused by a *Morbillivirus* of the paramyxovirus family, is one of the most contagious human infectious diseases, with a basic reproduction number (R_0) of 15–18 [1,2]. The worldwide disease burden is high, with the case fatality rate estimated at approximately one death per 1000 cases [3–5]. In 2009, there were 222,408 cases worldwide [6].

Given the availability of a highly-effective vaccine, highly-specific and sensitive diagnostic tests and the lack of animal reservoirs, some regions have adopted elimination targets. In the Americas, the 1994 Pan American Sanitary Conference established the goal of eliminating measles from the Americas, and the number of cases of measles was reduced by 99% in 1996 in comparison to 1990 levels [7]. Currently, measles is no longer endemic in the Americas and most countries have interrupted transmission of the virus [8].

The European Region of the World Health Organization set a goal of eliminating indigenous measles in the Region by 2010, but due to the increase of cases and outbreaks in the central and western parts of the Region, this goal has been postponed to 2015 [9]. Finland, where the coverage with two doses of vaccine was 95%, eliminated measles in 1993 [10]. However, as vaccination coverage with two doses is still suboptimal in some countries and population groups, the virus still circulates widely in Europe [11].

Abbreviations: R_0, basic reproduction number; MMR, measles mumps and rubella vaccine; VE, direct effectiveness of vaccination; RR, relative risks; AR_v, attack rate in vaccinated children; AR_u, attack rate in unvaccinated children; CI, confidence interval; R, effective reproduction number; EUVAC, European surveillance network for vaccine-preventable diseases.

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During the period 2005–2008, 120 outbreaks were reported in Europe, of which 17 reported more than 250 cases, with 25 deaths occurring [12].

In Catalonia, a region in north-eastern Spain with over seven million inhabitants, there was an outbreak of measles involving 381 cases between August 2006 and July 2007 due to a case imported from Bosnia [13]. The previous epidemic wave occurred in 1995, when 1860 cases were reported [14]. After this, cases appeared intermittently and irregularly, and between 2000 and 2005 there were only 25 cases reported (0.06/100,000 persons-year), due to high vaccination coverages. In 2006–2007, the incidence rate was 3.1/100,000 persons-year. The outbreak occurred mainly in the Barcelona-South Health Region, with a rate of 9.2/100,000 persons-year, and the majority of cases occurred in children aged less than 15 months. Seventy-nine percent of the cases occurred between October 2006 and January 2007.

The measles vaccine was introduced in 1978 in the publicly-funded vaccination schedule of Catalonia, for children at the age of 12 months. In 1980, the measles vaccine was replaced by a single dose of the combined measles, mumps and rubella vaccine (MMR) at 12 months. In 1987, the age of MMR administration was changed from 12 to 15 months, and in 1988 a second dose of MMR at 11 years was added. To ensure that the proportion of vaccinated children aged less than 10 years reached 95% and to achieve the elimination of measles by 2000, from the last quarter of 1998, the second dose of MMR was advanced to 4 years [15]. Therefore, at the time of the outbreak studied here, routine vaccination consisted of two doses of MMR at 15 months and 4 years, using the Schwarz (Priorix®) and Enders (MSD®) strains.

At the end of January 2007, to control the outbreak, in addition to post-exposure prophylaxis measures in the home and educational centres where cases appeared, a mass vaccination campaign was carried out consisting of the administration of one dose of MMR in children aged 9 to 12 months, with a second dose at 15 months.

The objective of this study was to evaluate the direct, indirect and total effectiveness of the measles component of the MMR vaccine in the context of a measles outbreak that affected mainly children attending day-care and pre-school centres and to estimate the number of cases that would have been avoided if the first dose of MMR vaccine had been administered at 12 rather than 15 months.

2. Materials and methods

2.1. Study population

We carried out a retrospective cohort study in educational centres in the Barcelona-South Health Region (population 2,853,658) attended by a confirmed case of measles during his infectiousness period with rash onset between 1st October 2006 and 15th January 2007. The temporal distribution of all cases of the outbreak is shown in Fig. 1. The study cut-off was established as 15 January 2007, in order to avoid possible bias due to the mass vaccination campaign. Centres where MMR administration within 72 h after exposure, which could have prevented cases of measles, were excluded [16]. The steps of this process are shown in Fig. 2.

A confirmed case of measles was defined as a laboratory-confirmed case (positive serology for measles immunoglobulin M antibody by enzyme-linked immunosorbent assay testing or positive polymerase chain reaction for measles virus in urine sample) or a case that met the WHO clinical case definition and was epidemiologically linked to a laboratory-confirmed case [17].

Children were considered as vaccinated against measles if they had received the MMR vaccine on or after the minimum recommended age for vaccination and at least 14 days prior to the onset of disease in the index case for each educational centre.

Susceptible children were defined as non-vaccinated children without measles infection before the outbreak.

Cases were investigated by public health staff. Active surveillance of children attending educational centres was carried out to detect secondary cases. Public health care centres provided written immunization records to regional public health staff, to determine previous vaccination or history of disease.

All children and educational staff who could not provide evidence of immunity were either vaccinated with the MMR vaccine or excluded and isolated at home until 21 days after the appearance of rash in the last reported case.

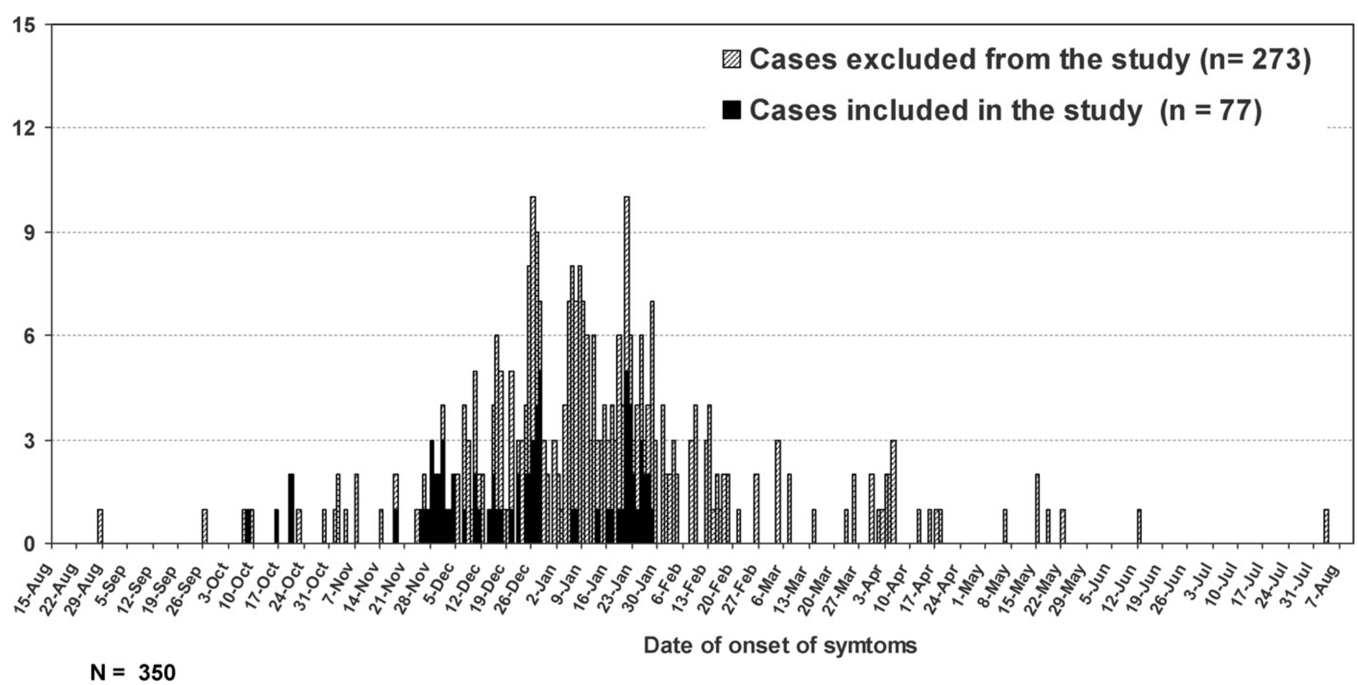

Fig. 1. Distribution of patients with measles according to date of onset of symptoms in Barcelona-South Health Region (August 2006 to July 2007).

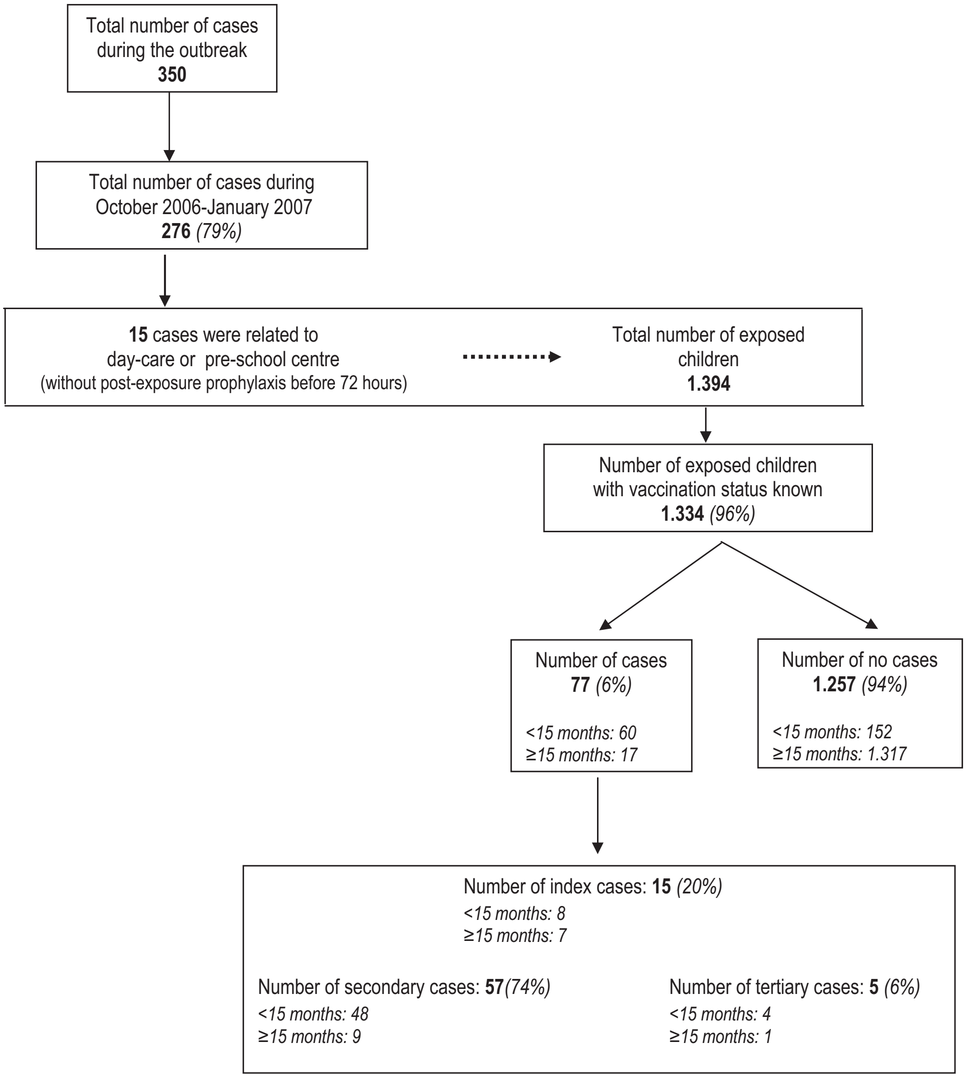

Fig. 2. Flow chart of measles cases according to day-care and pre-school centre. Barcelona-South Health Region, August 2006 to July 2007.

2.2. Vaccine effectiveness

To study direct vaccination effectiveness (VE), we excluded (a) children aged <15 months, (b) children with measles infection prior to the outbreak, and (c) children with unknown vaccination status.

Children vaccinated during the study period were classified according to the vaccination status before the outbreak.

According to the methodology described by Orenstein et al. [18], we estimated VE using the formula: $\mathrm{VE} = (1 - \mathrm{RR}) \times 100$, were RR is the rate ratio between the attack rate in vaccinated children ($\mathrm{AR_v}$) and the attack rate in unvaccinated children ($\mathrm{AR_u}$). The 95% confidence intervals (CI) were calculated using a Taylor series.

We also assessed the impact on effectiveness [19–21] using differences in vaccination rates in the following age groups according to the distribution of children in different classrooms: <6 months, 6–11 months, 12–23 months, 24–35 months and ≥36 months. Indirect effectiveness or herd immunity was estimated by comparing the risk in non-vaccinated children from an immunized population and an identical but fully unimmunized population. The formula $1 - \mathrm{AR_u}/\beta$ was used, where β is the baseline rate of disease that would occur in a different comparable population without immunization. In the case of measles, β is 1, since the disease would affect all susceptible children.

Total effectiveness (direct and indirect effect) was estimated by comparing the risk in vaccinated children from an immunized population versus an identical but fully unimmunized population, using the formula $1 - \mathrm{AR_v}/\beta$.

2.3. Basic reproduction number (R_0)

R_0 is the average number of secondary cases due to a single case introduced into a totally susceptible population [22]. To estimate R_0 we used Becker's deterministic model, using Eqs. (1) and (2) which include three parameters: the final number of cases (C), the number of susceptible children before the epidemic (S), and the total number of children attending the selected educational centres (N) [23].

$$\hat{R}_0 = \frac{N-1}{C} \sum_{i=S-C+1}^{S} \frac{1}{i}, \tag{1}$$

with standard error

$$SE(\hat{R}_0) = \frac{N-1}{C} \left(\sum_{i=S-C+1}^{S} \frac{1}{i^2} + \frac{C\hat{R}_0^2}{(N-1)^2} \right)^{1/2} \tag{2}$$

2.4. Effective reproduction number (R)

R is the average number of secondary infections per primary case in a population containing both immune and susceptible people. In a homogeneously-mixed vaccinated population we used the following equation:

$$[R = R_0 - (P \times R_0)] \quad (3)$$

where R_0 is the basic reproduction number, P the proportion of people vaccinated in the population and $(P \times R_0)$ the number of people protected [22,24].

In centres where the index cases only attended one day during the infectiousness period, there were only secondary cases in the same classroom. However, when they attended for more than one day, there were secondary cases in other classrooms. The estimates of R_0 and R were made for the centres where there were cases in other classrooms (Table 1: centres D–G, I, J, L and O).

2.5. Cases avoided by advancing the first dose of MMR to 12 months

The number of cases avoided was estimated using by calculating the basic reproduction number and the effective reproduction number, using Eq. (3).

2.6. Statistical analysis

The unit of analysis for this study was the individual child. A generalized linear mixed model was used to estimate the relationships between the previous vaccination status and the covariates age groups and gender. The following explanatory variables were considered as categorical: *vaccination status* (1 (reference value) = child unvaccinated, 2 = child had received one dose of measles-containing vaccine and 3 = child had received two doses); *age groups* (1 (reference value) = 15 months- < 4 years and 2 = ≥4 years); *gender* (1 (reference value) = male and 2 = female) and *educational centres* (each day-care or pre-school centre was assigned a category from 1 to 15).

Age groups and gender were the fixed effects and educational centres the random effects. These models can detect hypothetical clusters imposed by the variable educational centre.

Parameters were estimated using the library lme4 implemented on the *R* open source package [25].

Analyses were performed using the SPSS v18.0 for Windows and Epidat statistical packages.

3. Results

3.1. Characteristics of the study population

During the study period, we investigated 15 centres (12 day-care [0–3 years] and 3 pre-school [3–6 years] centres) with a total of 1394 children, of whom 51% (706) were male and with a median age of 27.3 months (range: 3.5–70.3). The characteristics of the centres investigated are shown in Table 1.

The vaccination status was determined in 1334 children (96%). The proportion of vaccinated children was 73.8% (range; 45.7–100%). Vaccination coverage was 91.6% in children aged ≥15 months (1121), 89.8% (774/862) in children aged 15 months- < 4 years and 97.7% (253/259) in children aged ≥4 years. There was a positive association between vaccination status and age groups ($p < 0.001$) but no association between vaccination status and gender ($p = 0.91$). There was no cluster effect imposed by the variable educational centre (variance = 0) (see Table 2).

No children with a history of measles were identified.

Table 1
Study children characteristics by day-care centres and primary schools. Barcelona-South Health Region, October 2006 to 15th January 2007.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Total
No of children attending	126	135	70	122	84	95	48	55	66	40	88	310	39	68	48	1394
Gender																
Male	65	66	38	70	45	48	26	26	34	21	45	149	19	30	24	706
Female	61	69	32	52	39	47	22	29	32	19	43	161	20	38	24	688
Age (median (min, max) in months)	21.6 (3.5–32.5)	49.2 (34.0–68.3)	51.5 (33.0–67.1)	21.9 (3.6–34.1)	25.2 (11.2–34.2)	25.5 (8.1–35.0)	16.6 (5.3–22.8)	25.1 (6.0–34.5)	28.8 (9.5–70.1)	23.3 (7.1–33.9)	37.9 (7.2–70.3)	27.3 (3.9–69.3)	22.1 (4.9–35.2)	57.3 (36.6–69.6)	18.3 (4.0–25.7)	27.3 (3.5–70.3)
Period of infectiousness (in days)	1	1	2	7	6	2	3	1	3	3	1	2	1	1	2	
Vaccination status																
0 dose	39	8	5	55	22	25	19	10	9	9	13	58	12	0	18	302
1 dose	83	71	35	61	62	67	16	44	37	14	51	212	27	27	28	835
2 doses	0	50	30	0	0	0	0	1	16	1	21	37	0	41	0	197
Missing information	4	6	0	6	0	3	13	0	4	16	3	3	0	0	2	60
Percentage of vaccinated	68.0%	93.8%	92.9%	52.6%	73.8%	72.8%	45.7%	81.8%	85.5%	62.5%	84.7%	81.1%	69.2%	100.0%	60.9%	77.4%
<6 months	0.0%	-	-	0.0%	-	-	0.0%	0.0%	-	-	-	0.0%	0.0%	-	0.0%	0.0%
6–11 months	0.0%	-	-	0.0%	0.0%	0.0%	0.0%	0.0%	20.0%	0.0%	0.0%	0.0%	0.0%	-	9.0%	1.7%
12–23 months	69.0%	-	-	51.8%	60.6%	59.4%	57.2%	81.3%	70.6%	60.0%	75.0%	75.0%	69.2%	-	75.0%	66.8%
24–35 months	97.7%	100.0%	83.3%	78.1%	89.4%	90.7%	-	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	-	100.0%	95.1%
>36 months	-	93.4%	93.7%	-	-	-	-	-	100.0%	-	97.6%	95.7%	-	100.0%	-	95.9%
Confirmed cases (n)	2	1	1	22	8	4	11	1	2	7	2	8	1	1	6	77
Attack rate (%)	1.6%	0.7%	1.4%	18.0%	9.5%	4.2%	22.9%	1.8%	3.0%	17.5%	2.3%	2.6%	2.6%	1.5%	12.5%	5.5%
Secondary cases	1	0	0	16*	7	3	10	0	1	6	1	7	0	0	5	57
Eligible for VE analysis in >15 months, n/cases	90/0	129/1	70/1	83/1	75/2	76/4	18/1	46/0	55/0	17/2	77/1	261/0	27/0	68/1	29/3	1121/17

* 5 tertiary cases are included.

Table 2
Generalized linear mixed model for estimating the relationships between the vaccination status and the covariates age group and gender using educational centres as cluster variable.

Formula: Previous Vaccination status ∼ Age + Gender + (1|Educational centre)				
Random effects				
Groups		Name	Variance	Std. dev.
Educational centre		(Intercept)	0	0
Number of obs: 1121, groups: Educational centre, 15				
Fixed effects				
	Estimate	std. Error	z value	Pr(>|z|)
(Intercept)	0.64039	0.03138	20.407	<2e−16***
Age2	0.35987	0.04511	7.977	1.49e−15***
Gender2	0.00470	0.04140	0.114	0.91

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '·' 1.

Regarding the distribution of children's age groups according to school classroom, the proportion of vaccines was: <6 months 0% (0/16), 6–11 months 1.7% (2/116), 12–23 months 66.8% (272/407), 24–35 months 95.1% (384/404), 36–47 months 92.4% (121/131) and ≥4 years 97.3% (253/260) ($p \leq 0.001$). Seventy-seven percent of children aged ≥4 years had received two doses.

Seventy-seven confirmed cases were detected (62 laboratory-confirmed and 15 due to epidemiological link), of which 54% (42) were male. Fifteen were index cases, 57 secondary cases and 5 tertiary cases. The median school attendance of cases during the infectiousness period was <1 day (range: 0–7 days) for all cases, 1 day (range: 1–7 days) for index cases and <1 day (range: 0–2 days) for secondary cases.

In 72 (93.5%) cases there was no history of vaccination or previous measles disease before the outbreak, while the remaining 5 cases had received one dose of MMR.

The global attack rate was 5.5% (77 cases in 1394 children) range, 0.7–22.9%. The attack rate in non-vaccinated children was much higher than in vaccinated children (24.0% versus 0.5%, $p < 0.001$). There were no cases in children vaccinated with two doses. The attack rate according to age group was 6.3% (1/16) in the <6 months age group; 22.4% (26/116) in the 6–11 months age group; 9.7% (42/433) in the 12–23 months age group; 1.1% (5/432) in the 24–35 months age group, and 0.7% (3/397) in the ≥36 months age group.

3.2. Vaccine effectiveness

3.2.1. Direct vaccination effectiveness

In the ≥15 months age group, 1121 children were eligible for the VE analysis, of whom 1027 were vaccinated (830 had received one and 197 two doses). The AR_u was 12.8% (12 cases in 94 non-vaccinated children) and the AR_v was 0.5% (5 cases in 1027 vaccinated children). The difference between AR_u and AR_v was statistically significant ($p < 0.001$). The VE for any dose of vaccine was 96.2% (95% CI: 89.4–98.6%), and was similar in children vaccinated with one dose, 95.3% (95% CI: 86.9–98.3%).

With respect to age groups, the VE was 89.4% (58.9–97.3%) in vaccinated children aged 15 to 23 months, 98.7% (88.9–99.8%) in those aged 24 to 35 months and 97.7% (76.1–99.8%) in those aged ≥36 months (Table 3).

3.2.2. Indirect vaccination effectiveness

Vaccination conferred herd immunity in unvaccinated children aged: 12–23 months 71.1% (95% CI: 63.5–78.8%), 24–35 months 80% (56.3–94.3%) and ≥36 months 88.2% (63.6–98.5%).

3.2.3. Total vaccination effectiveness

Total VE was 98.9% (96.8–99.8%) in vaccinated children aged 12–23 months and 99.7% (98.6–99.9%) in both the 24-35 months and ≥36 months age groups.

3.3. Basic reproduction number (R_0) and effective reproduction number (R)

Estimated R_0, using Eqs. (1) and (2), was 4.23 (95% CI: 2.79–5.66) for the eight centres where virus transmission was observed beyond the classroom of the index case.

The effective reproduction number (R) obtained from the initial proportion of susceptible children (30%) was 1.29 (95% CI: 0.85–1.72) at the beginning of the study and 0.75 (95% CI: 0.50–0.90) at the end of the study.

3.4. Cases avoided by advancing the first dose of MMR to 12 months

Of the 81 children aged 12 to 14 months studied, 33 were infected (attack rate 41%).

Table 3
MMR vaccination status, attack rate and direct vaccine effectiveness (VE) of children aged ≥15 months with known vaccination status, Barcelona-South Health Region, October 2006 to 15th January 2007.

	n	Cases	Attack rate, %	RR (95% CI)	VE, % (95% CI)	p
Vaccination status						
≥15 months	1121	17	1.5			
Non-vaccinated	94	12	12.8	1.0 (reference)	–	
Vaccinated	1027	5	0.5	0.04 (0.01–0.11)	96.2 (89.4–98.6)	<0.001
2-Doses	197	0	0	–	100.0	
1-Dose	830	5	0.6	0.05 (0.02–0.13)	95.3 (86.9–98.3)	<0.001
15–23 months	326	9	2.8			
Non-vaccinated	57	6	10.5	1.0 (reference)	–	
Vaccinated	269	3	1.1	0.105 (0.03–0.41)	89.4 (58.9–97.3)	<0.001
24–35 months months	404	5	1.2			
Non-vaccinated	20	4	20.0	1.0 (reference)	–	
Vaccinated	384	1	0.3	0.01 (0.003–0.1)	98.7 (88.9–99.8)	<0.001
≥36 months months	391	3	0.8			
Non-vaccinated	17	2	11.8	1.0 (reference)	–	
Vaccinated	374	1	0.3	0.02 (0.002–0.2)	97.7 (76.1–99.8)	<0.001

If these children had received the MMR vaccine at 12 months and assuming the same vaccination coverage in the study (91.6%) with an R_0 of 4.23, the number of children protected would have been 3.87 (91.5% of 4.23); using equation 3 [4.23 – (0.916 * 4.23)] the value of R obtained would be 0.36, and therefore 8.5% of children would have developed measles (7 cases) and 74 cases would have been avoided.

4. Discussion

This outbreak illustrates the current epidemiology of measles in Spain where, thanks to high MMR vaccine coverage, there is no endemic measles transmission, but there is a risk of outbreaks due to imported cases, as shown by the outbreak referred here, which was due to an imported case that generated small clusters of short duration in unvaccinated people. The difficulty in implementing adequate infection control measures in less than 72 h outside the family environment may have contributed to the appearance of these clusters [16].

The size of an outbreak depends on both the proportion of susceptible individuals in the population and on chance events in the transmission process. Therefore, countries and regions with measles elimination strategies should monitor mean outbreak sizes as an indicator of the elimination status [17,26].

In our study, the highest attack rate was in children aged 6–11 months (22.4%), followed by those aged 12–23 months (9.7%). Given the vaccination schedule when the outbreak occurred and the distribution of children in educational centres, it may be suggested that children aged 6–11 months had no immunity because they had not previously been infected (no circulation of the virus), were not vaccinated because of the vaccination schedule and had no maternal immunity. The percentage of susceptible children in this age group was 98.3% and, for the reasons mentioned above, we consider that herd immunity in the context of educational centres was virtually non-existent.

In the 12–23 months age group, vaccinated and non-vaccinated children shared classrooms. In vaccinated children, the VE was 89%, but herd immunity could only prevent 71% of the expected cases in unvaccinated children and was totally inadequate in preventing the spread of the outbreak.

In the 24–35 months and ≥36 months age group, only 5% of children were susceptible to measles, because 70.7% had received one dose of MMR and 24.7% two doses. There was lower transmission of measles in the classroom (global attack rate of 0.9%), due to the high VE in vaccinated children and a herd immunity of nearly 90%.

The fact that 93.5% of cases were children non-vaccinated due to age meant that most of their school contacts were also non-vaccinated children. Therefore, the two main control measures consisted of advancing the first dose of MMR in susceptible exposed children aged 9 to 12 months and the isolation of symptomatic children. With respect to post-exposure vaccination, vaccination within 72 h after exposure was not possible in any centre, but susceptible children were vaccinated to avoid tertiary and quaternary cases. This intervention could only be carried out from mid-January onwards, after a public information campaign on measles prevention. Therefore, the previous control measure that allowed the spread of the outbreak to be controlled was principally active surveillance of exposed people in order to isolate cases (a child with fever should not attend the centre).This measure reduced the median period of transmissibility from 1 day (1–7) to less than 1 day (0–2), allowing the transmission chain to be broken.

These community-based interventions require immediate and effective action by field epidemiology surveillance units and therefore robust and sensitive surveillance systems, coordinated with medical services, are essential.

The control measures mentioned above affect the transmission of the virus. In our study, the estimated R_0 was 4.3 (95% CI 2.8–5.7), lower than that found by other reports in vaccinated populations, although these studies did not state whether cases were isolated. The isolation of cases may explain the reduced transmission observed in our study [27,28]. It is accepted that, to eliminate measles, the value of R_0 should be below unity. The reduction in the infectious period achieved by isolating cases limited the spread of the outbreak in schools, reducing the effective reproduction number to <0.7 (95% CI 0.5–0.9), the level recommended by the WHO.

In our study, the VE with one dose of MMR in children aged ≥15 months was 95% (87–98%) and 100% in children vaccinated with two doses. These data are consistent with studies of previous outbreaks [29–31] and confirm that vaccination with two doses of MMR is highly-effective in preventing measles [32–34].

When this outbreak began in Catalonia, the administration of MMR at 15 months was recommended, based on studies of immunogenicity and protective efficacy carried out in the 1970s and 1980s that showed that the risk of contracting measles in children vaccinated at 12 months was 1.5–5 times higher than in those vaccinated after this age [35–37].

Recent studies show that, in populations with high vaccine coverages, the probability of natural boosting is reduced, causing an earlier loss of passive acquired immunity due to an earlier decrease in maternal antibodies transferred after 6 months of age in children both of vaccinated women and of women with naturally-acquired immunity. This leads to an increasing gap in susceptibility between the loss of maternal antibodies and administration of the first MMR dose [38–40]. On-time delivery of the first dose remains the highest priority for elimination programmes, and should be administered as soon as possible after the loss of protection by maternal antibodies. The current WHO recommendation in countries with low rates of measles transmission is that the first dose may be administered at 12 months [41].

Analysis of the outbreak led health authorities to recommend the systematic advancement of the MMR vaccination from 15 to 12 months from 2008 onwards [42]. Assuming the same coverage of children vaccinated (91.6%), if vaccination at 12 months had been carried out, the effective reproduction number would have been 0.4, meaning that 8.5% of children would have been infected. This means that, in the 81 children aged 12–14 months, there would have been 7 cases instead of 33, and therefore 32% (26/81) of cases would have been prevented and the attack rate in this age group would have been 8.6% instead of 41%.

The evolution of measles in our region after the outbreak studied confirms this approach. In December 2010, a new outbreak of measles due to an imported case was detected in our region. Between December 2010 and July 2011, 92 confirmed cases have been detected with a median age of 26 years (range 2 months-46 years) [43]. Eighty-four percent were non-vaccinated people, 25% of them were <12 months and 62% ≥15 years. No transmission in educational centres has been observed in children over 12 months. In the period December 2006 to February 2007, when the MMR was administered at 15 months, there were 52 confirmed cases in children 12–15 months. The huge difference between the two outbreaks (52 cases when the vaccine was administered at 15 months and only 1 when administered at 12 months) is probably due to the increase in the proportion of children vaccinated in this age range.

At present, only 34.4% of countries included in the EUVAC network include routine administration of the first dose of MMR at 12 or 13 months, while 37.5% administer it at different ages from 14 months onwards, including some at 18 months, while 28.1% have a recommended interval between a lower limit of 11–13 months and an upper limit of 14–24 months [44]. Thus, there may be children vaccinated after 13 months of age in accordance with national vaccination schedules. This is the situation in Spain, where the national vaccination schedule establishes an interval for the first dose of between 12 and 15 months: however, only 3 of the 19 Spanish regions vaccinate at 12 months [45] while the remaining 16 vaccinate at 15 months. In Europe, more than half the EUVAC countries recommend the first dose of MMR after 13 months. As the measles virus circulates widely in Europe and outbreaks continue to emerge in different EU countries, in addition to achieving and maintaining very-high vaccination coverages (≥95%) of each new birth cohort with two doses of MMR, it would be desirable to administer the first dose at 12 months.

Some potential limitations of this study might bias the calculation of vaccine effectiveness [18], including the verification of vaccination and the underdetection of cases. However, the vaccination status was verified directly by public health staff and a follow-up was conducted in each centre until the end of the outbreak to capture all cases. Therefore, we believe that these factors had no influence.

Likewise, another possible limitation is that the method for estimating R_0 assumes no heterogeneity in mixing. This means that every child has the same probability of contact with other children. R_0 was calculated in centres attended by the index case for two or more days during the infectious period, ensuring the possibility of contact between children. Vaccinated and non-vaccinated people are not distributed at random. We did not use stochastic models, as the study population was closed with only two generations of cases.

5. Conclusions

Direct vaccine effectiveness after receiving at least 1 dose of MMR vaccine was high (>96%). However, the outbreak could not be avoided due to the large number of exposed children who had not reached the recommended vaccination age. It is important to monitor the changes in the fraction of susceptible individuals over time.

If the first dose of MMR vaccine had been administered at 12 instead of 15 months, 91.5% of cases in children aged 12 to 14 months would have been avoided. In order to achieve the goal of eliminating measles in Europe, we consider it essential to advance the first dose of MMR to 12 months, as recommended by the WHO.

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