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Lack of herd immunity against measles in individuals aged <35 years could explain re-emergence of measles in Catalonia (Spain)

Pedro Plans [a,b,*], Nuria Torner [a,b], Pere Godoy [a,b], Mireia Jané [a]

[a] Public Health Agency of Catalonia, Department of Health of Catalonia, Bac de Roda 83–85, 08005 Barcelona, Spain
[b] CIBER – Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain

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SUMMARY

Objectives: The objective of this study was to assess the association between lack of herd immunity in some population groups and the re-emergence of measles in Catalonia in 2006.
Methods: Herd immunity was considered established in the different population groups when the prevalence of positive serological results to measles was higher than the herd immunity threshold of 90%. The Chi-square test and the odds ratio were used to assess the association between lack of herd immunity and measles cases in the outbreak of 2006–2007.
Results: Herd immunity was not established against measles in individuals aged 0–14 years and 25–34 years, as the prevalence of positive serological results was <90% in these groups. In the measles outbreak of 2006–2007, 91% of cases occurred in age groups without herd immunity, and only 9% of cases occurred in age groups with herd immunity ($p < 0.001$). The odds ratio for the association between lack of herd immunity and measles cases in the outbreak of 2006–2007 was 104 ($p < 0.001$).
Conclusion: Lack of herd immunity in individuals aged < 35 years could be one of the factors underlying the re-emergence of measles in Catalonia.

1. Introduction

In 2010, the World Health Organization (WHO) European Region renewed its commitment to the elimination of measles by 2015, but measles cases and outbreaks are still occurring in many European countries.[1–4] The highest ever reported incidence of measles in the WHO European Region since measles surveillance was implemented through the EUVAC.NET system, occurred in 2011.[3,4] The EUVAC.NET surveillance system was established in 1999 for selected vaccine-preventable diseases.[2] It incorporated all European Union Member States together with Iceland, Norway, Switzerland, and Turkey.

In Catalonia, an autonomous region of Spain with seven million inhabitants, indigenous measles virus transmission was interrupted in 2000, but a measles outbreak involving 381 cases was declared in 2006.[5] Analysis of the epidemiological characteristics of the outbreak showed that 94% of cases occurred among individuals aged <35 years, and 89% occurred among unvaccinated individuals.[5] The re-emergence of measles in Catalonia in 2006–2007 could be explained by the mobility of people carrying measles infections from infected areas or countries to Catalonia, and the lack of the necessary herd immunity to block measles transmission in the population. The herd immunity theory proposes that in diseases passed from person-to-person, the chain of infection is blocked when the prevalence of protected individuals in the population is higher than a disease-specific threshold, known as the herd immunity threshold (I_c).[6–9] The objective of this study was to assess the association between lack of herd immunity in some population groups and the re-emergence of measles in Catalonia in 2006–2007.

2. Methods

The association between lack of herd immunity and measles cases in the outbreak of 2006–2007 was assessed by means of comparing the distribution of measles cases in age groups with and without herd immunity in 2006–2007 in Catalonia. The Chi-square test and odds ratio (OR) were used to assess this association, considering $p < 0.05$ as statistically significant. The following age groups were considered in the analysis: 0 months, 1–8 months, 9–14 months, 15 months–4 years, 5–9 years, 10–14 years, 15–24 years, 25–34 years, and ≥35 years.

Herd immunity was considered established in different population groups in 2006–2007 when the prevalence of positive

* Corresponding author. Tel.: +34 935 513682; fax: +34 935 517506.
E-mail address: pedro.plans@gencat.cat (P. Plans).

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serological results to measles (p) was higher than the mean critical prevalence of positive measles results associated with herd immunity (p_c): $p > p_c$.[6–8] The value of p_c was determined using the formula $p_c = I_c\,Se + (1 - I_c)(1 - Sp)$, where I_c is the critical prevalence of protected individuals blocking measles transmission,[6,7] and Se (=97%) is the sensitivity and Sp (=97%) is the specificity of the ELISA test used in the serological survey of 2002 (Measles ELISA Test, Wampole Laboratories, Cranbury, NJ, USA).[6,7] The value of I_c was determined using the formula: $I_c = 1 - (1/R_o)$, where R_o is the basic reproductive number. The value of R_o for measles viruses ranges from 11 to 18.[9]

The prevalence of positive serological results in the different age groups aged ≥5 years in 2006–2007 was determined using SPSS v. 18 (SPSS Inc., Chicago, IL, USA) by taking into account serological results obtained in the surveys of 2002 and the age increase between 2002 and 2006. The seroepidemiological surveys carried out in Catalonia in 2002 included a representative sample of 1324 individuals aged 5–14 years, a representative sample of 1295 individuals aged ≥15 years, and a representative sample of 1498 neonates (0 months).[6,7,10] Serological analysis for measles was carried out in the Laboratory of Microbiology of the Hospital Clinic of Barcelona. The presence of IgG measles antibodies was determined using the measles IgG ELISA (Wampole Laboratories); values >0.16 IU/ml were considered positive, values <0.12 IU/ml were considered negative, and values between 0.12 and 0.16 IU/ml were considered equivocal.[6,7,10] Samples with equivocal results were retested to confirm the initial result. Samples nonreactive in the second test were considered negative.

The prevalence of positive measles results in individuals aged 0–14 months and 15 months–4 years in 2006 depended on passive immunity and vaccine-induced immunity, respectively, because the measles–mumps–rubella (MMR) vaccine was given at 15 months and 4 years.[5,6] The prevalence of positive serological results in neonates (0 months) in 2006 was determined assuming that neonates in 2006 would not be different to those included in the representative sample of neonates obtained in 2002.[10] Consequently, the prevalence of positive serological results (98.5%)[10] observed in neonates in 2002 was assumed for neonates in 2006. The prevalence of positive serological results in individuals aged 1–8 months in 2006 was determined assuming that this prevalence would be 50% of the prevalence observed at 0 months, since maternal antibodies endure for a median of 3 months.[11] The prevalence of positive serological results observed in a sample of 51 infants aged 9–14 months (37.7%) studied in Catalonia in 2007[12] was assumed for individuals aged 9–14 months in 2006.

The prevalence of positive measles results in individuals aged 15 months–4 years, not included in the seroepidemiological surveys of 2002, was determined using the formula $p = I\,Se + (1 - I)(1 - Sp)$, where I is the prevalence of protected individuals due to vaccination in this age group in 2006.[6] The value of I in this age group was determined by multiplying the vaccination coverage in individuals aged 1 year, 2 years, 3 years, and 4 years in 2006[13] by the measles vaccine effectiveness, adjusting the value of I for each year by the proportion of individuals in the group: $I = (I_{1\ year} \times 0.266) + (I_{2\ years} \times 0.252) + (I_{3\ years} \times 0.241) + (I_{4\ years} \times 0.241) = (V_{1\ year} \times E_{1\ dose} \times 0.266) + (V_{2\ year} \times E_{1\ dose} \times 0.252) + (V_{3\ year} \times E_{1\ dose} \times 0.241) + (V_{4\ year} \times E_{2\ doses} \times 0.241)$. Vaccine effectiveness of 92% was assumed for preventing secondary cases of measles in individuals aged 1–3 years (1 dose) and 95% in those aged 4 years (2 doses).[14]

3. Results

The estimated prevalences of positive serologic results to measles in the different age groups in Catalonia in 2006 are presented in Table 1. The estimated prevalence of positive measles results in 2006 was higher than 92% only in individuals aged 15–24 years and ≥35 years. The estimated prevalence of positive measles results in individuals aged 15 months–4 years was 86.8%. This prevalence was obtained taking into account an MMR vaccination coverage in 2006 of 96.8% in individuals aged 15 months, 97.3% in those aged 2 years, 96.7% in those aged 3 years, and 96.7% for the first dose and 94.1% for the second dose in those aged 4 years.[13]

Table 1
Prevalence (%) of positive serological results to measles in Catalonia in 2006, establishment of herd immunity in different age groups, and association between lack of herd immunity and measles cases in the outbreak of 2006–2007

Age group	Herd immunity levels in Catalonia in 2006				Distribution of measles cases in the outbreak of 2006–2007	
	Prevalence of positive serological results to measles			Establishment of herd immunity:[a] Pos, prevalence >90% Neg, prevalence <90%		
	%	95% CI	*n*		No.	%
0 months	98.5	97.8–99.1	1498	Pos	0	0.0
1–8 months	49.2	46.6–51.8	1498	Neg	28	7.4
9–4 months	37.7	25.5–49.8	51	Neg	148	38.8
15 months–4 years	86.8	85.0–88.5	1498	Neg	80	21.0
5–9 years	85.5	80.9–90.1	228	Neg	13	3.4
10–14 years	89.9	87.0–92.8	455	Neg	10	2.6
15–24 years	92.5	90.8–94.3	926	Pos	10	2.6
25–34 years	89.3	84.9–93.6	214	Neg	68	17.9
≥35 years	98.3	97.5–99.2	1022	Pos	24	6.3
Total No. of individuals in age-groups without herd immunity					347	91.1[b]
Total No. of individuals in age-groups with herd immunity					34	8.9
OR (95% CI)					104.2 (63.4–171.2)[b]	
OR (95% CI) in individuals aged ≥5 years					7.2 (4.1–12.5)[b]	

OR, odds ratio; CI, confidence interval.

[a] Herd immunity against measles was considered established (Pos) when the estimated prevalence of positive serological results (p) was higher than the mean critical prevalence associated with herd immunity (p_c = 90%). The value of p_c was determined using the formula $p_c = I_c\,Se + (1 - I_c)(1 - Sp)$, where I_c is the critical prevalence of protected individuals blocking measles transmission, Se (=97%) is the sensitivity, and Sp (=97%) is the specificity of the serological test. The value of I_c for measles viruses ranges from 91% to 94% and p_c ranges from 89% to 91% (mean 90%).

[b] $p < 0.001$.

The herd immunity threshold in terms of critical prevalence of protected individuals (I_c) ranged from 91% to 94%. The herd immunity threshold in terms of critical prevalence of positive serological results to measles (p_c) ranged from 89% to 91%, with a mean value of 90%. Based on the critical prevalence of positive measles results, herd immunity could not be established in 2006 in individuals aged 0–35 years, except in those aged 15–24 years, while it could be established in individuals aged ≥35 years. The analysis of the distribution of measles cases detected in the outbreak of 2006–2007 showed that measles cases were more frequent in age groups without herd immunity (91%) than in those with herd immunity (9%), with statistically significant differences ($p < 0.001$) (Table 1). The OR for measles in age groups without herd immunity was 104 ($p < 0.001$) (Table 1). The OR for measles in age groups ≥5 years without herd immunity was 7.2 ($p < 0.001$).

4. Discussion

This study shows that lack of herd immunity in individuals aged <35 years could be one of the factors underlying the re-emergence of measles in Catalonia in 2006–2007, as most measles cases occurred in age groups without herd immunity. In individuals aged 15 months–24 years, insufficient herd immunity levels could be explained by insufficient vaccination coverage and/or insufficient vaccine effectiveness, while in those aged 25–34 years (unvaccinated),[6] insufficient herd immunity levels could be explained by a lower circulation of measles viruses since 1981, when the measles vaccination program was introduced in Catalonia.

The transmission of measles was interrupted in Catalonia in the year 2000, and during the period 2000–2005, measles cases were related to imported cases and no transmission chains involved indigenous individuals.[5] The measles outbreak of 2006–2007 occurred because one imported measles case infected population groups without sufficient herd immunity. Between 2000 and 2005, measles transmission did not include indigenous individuals for one of the following two reasons. First, imported measles cases did not come into contact with indigenous population groups without herd immunity. Second, the prevalence of indigenous and non-indigenous susceptible individuals aged <35 years could have been higher in 2006 than in previous years due to waning vaccine-induced immunity or lower vaccine effectiveness in the period 2000–2006.

The WHO European Region proposed eliminating measles by 2010, but the persistence of the disease in many European countries made it impossible to achieve this objective.[1] The elimination of measles is a feasible objective for the following reasons: (1) humans are the only reservoir for measles viruses; (2) effective vaccines are available for measles; (3) highly sensitive and specific diagnostic tests are available; and (4) efforts can be combined in order to eliminate measles, mumps, and rubella.[7] Nevertheless, the elimination of measles from Catalonia and Europe requires that a high prevalence of protected individuals is achieved and maintained in order to prevent outbreaks from imported cases.[6–8]

In the future, the number of adults susceptible to measles could increase in Spain and other countries if the duration of vaccine-induced immunity is lower than the duration of immunity from natural infection. In this situation, serological surveillance systems should be implemented in order to identify and immunize population groups without herd immunity.[7] Herd immunity could be established in these groups by means of additional vaccinations. Based on this preventive strategy, three complementary vaccination programs could be developed: (1) to vaccinate only susceptible individuals identified using pre-vaccination screening ('catch-up of susceptibles' strategy); (2) to vaccinate all individuals, regardless of their vaccination and disease status ('catch-up' strategy); and (3) to vaccinate individuals who have no documentation of completed vaccination, unless they have laboratory evidence of immunity to measles, documentation of provider-diagnosed measles, or a medical contraindication to the vaccine.[7] The 'catch-up of susceptibles' strategy is the best complimentary vaccination program for countries with high percentages of vaccination coverage. The 'catch-up' strategy is the best preventive strategy for countries with low percentages of vaccination coverage and/or low vaccination effectiveness. The third strategy can be developed only in countries with excellent vaccination registries; however, the main problem of this preventive strategy is that susceptible individuals due to primary vaccination failures could be identified and immunized.

In conclusion, a lack of herd immunity could be one of the factors explaining the re-emergence of measles in Catalonia (Spain) in 2006. In Spain and other countries with high percentages of measles vaccination coverage, serological surveillance systems could be developed to detect population groups without herd immunity, and additional vaccinations could be recommended in these groups to prevent measles cases and outbreaks.

Conflict of interest: No conflict of interest to declare.

Ethical approval: Informed consent was obtained from all participants in the seroepidemiological surveys carried out in Catalonia in 2002.

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