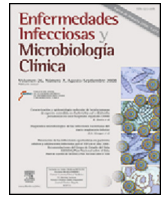




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Original article

Epidemiology of measles in vaccinated people, Spain 2003–2014[☆]



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ABSTRACT

Introduction: During the final phase of measles elimination rigorous investigation of each individual case becomes fundamental to confirm or discard cases, particularly among vaccinated people, since they experience a milder disease, and laboratory diagnosis is more complex. Our study focused in the epidemiology of measles in vaccinated people.

Methods: Longitudinal study on measles cases in two dose vaccinated people in Spain from 2003 to 2014. **Results:** We confirmed 138 measles cases (90 of them, laboratory confirmed) in people with two doses of vaccine. The median of time from last vaccination to rash onset showed a lineal trend ($p < 0.001$), in parallel with the number of doses of vaccine received (0, 1, 2 doses). Among confirmed cases, the hospitalisation risk decreased inversely proportional to the number of administered vaccine doses (linear trend, $p < 0.001$). Only in 23.9% of confirmed cases and 50% of discarded cases the guidelines about sample taking were fulfilled. 50% of samples in two dose vaccinated people were taken without fulfilling time delay criteria. 16.7% (36/215) of discarded cases with a negative IgM result did correspond to samples taken early (first 72 h after rash) and could represent false negatives.

Conclusion: Our results highlight the importance of fulfilling properly the guidelines for laboratory diagnosis in order to confirm or discard every measles case, especially in two dose vaccinated people. When a negative IgM result is obtained in early samples a new IgM test should be practiced, as well as a PCR test, in order to avoid infra-detection of cases.

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Epidemiología del sarampión en personas vacunadas, España 2003–2014

RESUMEN

Introducción: En la fase de eliminación del sarampión, reviste especial importancia la investigación de cada caso sospechoso, especialmente en personas vacunadas, pues en ellas la clínica es más leve, y los resultados de laboratorio más difíciles de interpretar. Nuestro estudio se centró en la epidemiología del sarampión en personas vacunadas.

Métodos: Se realizó un estudio longitudinal de los casos de sarampión en personas vacunadas notificados en España entre 2003 y 2014.

Resultados: Se observaron 138 casos confirmados de sarampión en personas vacunadas con 2 dosis, 90 de ellos confirmados por laboratorio. La mediana de tiempo entre la última dosis de vacuna recibida

Palabras clave:

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y la aparición del exantema mostró una tendencia lineal creciente ($p < 0,001$) en función de las dosis de vacuna (0, 1, 2 dosis). El riesgo de hospitalización disminuyó de forma inversamente proporcional al número de dosis de vacuna recibidas ($p < 0,001$). Solo en el 23,9% de los casos confirmados y en el 50% de los descartados, se cumplió el protocolo de recogida de muestras clínicas. En el 50% de los casos estudiados en vacunados con 2 dosis, las muestras se tomaron precozmente. El 16,7% de los descartados mediante IgM negativa podrían ser falsos negativos, pues procedían de muestras precoces.

Conclusión: Nuestros resultados evidencian la importancia de cumplir el protocolo diagnóstico para confirmar o descartar casos de sarampión, especialmente en los vacunados con 2 dosis. Ante una IgM negativa en muestras precoces, sería necesario obtener una nueva muestra y realizar un nuevo test de IgM, así como la prueba de PCR.

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Introduction

In recent decades we have witnessed a dramatic reduction in the morbidity and mortality associated with measles thanks to the generalised use of the vaccine.¹ Measles is an eliminable disease because its reservoir is exclusively human, it is difficult for the agent to survive in the atmosphere and in addition to good diagnostic techniques, there is an effective and economical vaccine that induces lasting immunity.² Elimination entails interrupting the endemic transmission of the measles virus in a region for at least 12 months, under a high quality surveillance system.³ The European Region of the World Health Organisation (WHO) set the objective of eliminating measles in 2015.^{4,5} This study falls within the Spanish National Plan for the Elimination of Measles and Rubella,⁶ included in the European strategy for the elimination of measles and rubella.^{5,7} Despite efforts, in recent years, various outbreaks of measles have been reported in Spain and in other European countries,^{8–10} most between 2010 and 2012.

In areas with high vaccine coverage, a new case of measles generates few secondary cases, but a major proportion of these will be people who have been vaccinated.¹¹ In these cases, the disease might be due to primary vaccine failure (no initial response) or secondary vaccine failure (due to waning immunity, or, less commonly, due to their antibodies' lack of neutralising capacity). Waning implies an attenuated immune response, not sufficient to prevent the disease, because the levels of measles-specific antibodies are lower in vaccinated individuals than in those exposed to the wild virus.^{12,13} In vaccinated persons, measles is less contagious and the symptoms are milder.^{14,15}

The main strategies of the WHO to accelerate the elimination of measles in the European Region are to maintain the population's immunity to measles, reinforce the surveillance protocol (investigating each suspicious case in a timely and thorough manner in the laboratory), establish means for controlling transmission, establish the circulation of the virus, and verify its elimination.^{3,6}

In vaccinated persons, it is more difficult to confirm or discard suspicious cases, since the viral load is less, and serology for IgM in the first days after onset of the rash might be negative, even in true measles cases. Some studies recommend complementing routine diagnostic methods with techniques such as the high IgG avidity test, or the IgG quantitative test.^{15,16} In the final phase of elimination, with very low incidence rates, suspected measles in vaccinated persons must be thoroughly investigated, especially if they have received 2 doses of the vaccine.

The principal objective of the study was to analyse the features of suspected measles in persons vaccinated with two doses, notified to the Spanish National Plan for the Elimination of Measles between 2003 and 2014, and to examine how the laboratory procedures (taking clinical samples and tests performed) adapt to the current surveillance protocol.

Methodology

Following the measles surveillance protocol¹⁷ of the National Epidemiological Surveillance Network (RENAVE), we used the following case definitions:

- Laboratory-confirmed case: meets clinical and laboratory criteria, not recently vaccinated (21 days before onset of the rash), or recently vaccinated but presenting the wild genotype of the virus. Confirmation is by positive IgM in serum (of choice) and/or positive PCR in urine/pharyngeal exudate.
- Epidemiological link confirmed case: meets the clinical criteria and has an epidemiological link with a laboratory-confirmed case.
- Clinically compatible case: meets the clinical criteria but not possible to take samples for serological confirmation, and there is no epidemiological link with a laboratory-confirmed case. In large outbreaks (2010–2012), given the difficulty of investigating all the cases in the laboratory, a large part were classified as “clinically compatible”, meaning they were highly likely to be true cases of measles. These cases were considered “confirmed” in the analysis.
- Discarded case: meets the clinical criteria for measles, with negative laboratory results or with epidemiological link with a laboratory-confirmed case of another exanthematous disease. A negative IgM result results in a case being discarded. A negative PCR, on its own, does not result in a case being discarded.
- All suspected cases of measles should be notified and investigated, taking timely samples of serum (from the fourth day after onset of the rash, but never later than the twenty-eighth day), and urine and/or pharyngeal exudate (within 7 days of onset of the rash). If the IGM is negative in serum collected in the first 72 h a second sample must be taken between days 4 and 28, in the absence of another confirmatory result.¹⁷

A retrospective, cohort study was designed that included all suspected cases of measles notified to the Spanish National Plan for the Elimination of Measles between 2003 and 2014. Layers were created according to vaccination status, age group and case classification (confirmed/discarded). The incidence of measles was calculated by age group, relative risk (RR) of confirmation of measles in suspected cases according to age group and the number of vaccine doses received, as well as the RR of hospitalisation in confirmed cases. The RR with its confidence interval was calculated based on the odds ratio (OR), using Kleinbaum's method for rare diseases.¹⁸ The variables studied were: year, case classification, age, age group (<5 years, 5–19 years, 20 years or older), date of rash onset, hospitalisation, number of vaccine doses (a vaccine dose administered at least 21 days prior to onset of rash was considered valid, this is the time required for the immune response to develop), date of last vaccine dose, difference in years between the date of the

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