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6. Epidemiology of measles virus outbreaks in Catalonia : Importance of immunization in the elimination era

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Abstract. Eradicating measles represents a major public health achievement, yet outbreaks still occur in territories where endemic measles virus (MV) had been eliminated. In Catalonia from the year 2000 cases have occurred as isolated cases or small outbreaks, both linked to imported cases up to the end of 2006 when a large outbreak started out affecting mainly children ≤15m. In consequence, immunization schedule was amended lowering first dose to 12m. Again new MV importations from neighboring countries triggered another outbreak on November 2010 with a different age distribution sparing small children from infection. Differences in incidence (IR), rate ratio (RR) and 95% CI and hospitalization rate (HR) by age group were determined. Statistic z was used for comparing proportions. Total number of confirmed cases was 305 vs 381 in 2006; mean age 20 yrs (SD 14.8yrs; 3m -51yrs) vs 15m (SD13.1yrs; 1m-50yrs). Highest proportion of cases was set in ≥25yrs (47%) vs 24.2% in 2006 ($p<0.001$). Difference in

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IR for $\leq$ 15m was statistically significant (49/100,000 vs 278.2/100,000; RR:3.9; 95%CI 2.9-5.4) and in HR 30.2% vs 15.7% ($p<0.001$). The change of the month of administration of the first dose proved successful. Given the current epidemiological situation, continued awareness and efforts to reach young adult population are needed to stop the spread of the virus.

Introduction

Eradicating measles represents a major public health achievement, yet outbreaks still occur in territories where endemic measles virus (MV) had been eliminated. In theory, if the right tools were available, all infectious diseases would be eradicable. In reality, there are distinct biological features of the organisms and technical factors of dealing with them that make their potential eradicability more or less likely. Today's categorization of a disease as not eradicable can change completely tomorrow, either because research efforts are successful in developing new and effective intervention tools or because those presumed obstructions to eradicability that seemed important in theory prove capable of being overcome in practice. Three indicators were considered to be of primary importance: an effective intervention is available to interrupt transmission of the agent; practical diagnostic tools with sufficient sensitivity and specificity are available to detect levels of infection that can lead to transmission; and humans are essential for the life-cycle of the agent, which has no other vertebrate reservoir and does not amplify in the environment [1].

The effectiveness of an intervention tool has both biological and operational dimensions. Elimination validates the effectiveness of an intervention tool, but it does not necessarily make the agent a candidate for eradication. Highly developed levels of sanitation and health systems development may make elimination possible in one geographical area but not in another.

Diagnostic tools also have both biological and operational dimensions. The tools must be sufficiently sensitive and specific to detect infection that can lead to transmission, and also sufficiently simple to be applied globally by laboratories with a wide range of capabilities and resources. Eradication is a much more feasible target of deliberate intervention when humans form an essential component of the agent's life-cycle. An independent reservoir is not an absolute barrier to eradication if it can be targeted with effective intervention tools.

The costs and benefits of global eradication programmes can be grouped into two categories: direct effects and consequent effects. The direct effects of eradication are that no morbidity or mortality due to that disease will ever again occur. Explicit efforts should be taken to maximize the effectiveness of both eradication and comprehensive health programmes [2].

Eradication has been defined in various ways: as extinction of the disease pathogen, as elimination of the occurrence of a given disease, even in the absence of all preventive measures, as control of an infection to the point at which transmission ceased within a specified area, and as reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts, obviating the necessity for further control measures. The hierarchy of potential public health efforts in dealing with infectious diseases was discussed at the Dahlem Workshop. Differences in these efforts made a distinction between the disease caused by the infection and the infection itself, the level of reduction achieved for either of these, the requirement for continuation of control efforts, and, finally, the geographical area covered by the intervention efforts and their outcomes. Although definitions outlined below were developed for infectious diseases, those for control and elimination apply to noninfectious diseases as well [3].

Control: The reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. Example: diarrheal diseases.

Elimination of disease: Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts; continued intervention measures are required. Example: neonatal tetanus.

Elimination of infections: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required. Example: poliomyelitis.

Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed. Example: smallpox.

Extinction: The specific infectious agent no longer exists in nature or in the laboratory. (There is no example yet) [2].

Globally, about 25% of disease morbidity and mortality are attributable to communicable diseases. In developed countries communicable diseases have decreased in a remarkable way because of antibiotics and vaccines.

One of these candidate diseases to be eliminated and ultimately eradicated is measles [4]. Measles is a highly transmissible disease for which conditions for eradication are favorable: humans are the only reservoir for the measles virus (MV), the vaccine is safe, inexpensive and produces life-long immunity, diagnostic tests are both specific and sensitive, all infected people develop symptoms, and there are no chronic carriers [4,5]. Eradicating measles would represent a major public health achievement, well worth the investment it requires. For the EU, the first step towards eradication of measles is effective control within its own borders. Finally, eradication will be the result of elimination of transmission on all continents. Elimination of measles by 2015 is part of the WHO strategic plan for measles in the World Health Organization (WHO) European Region.

Measles is caused by a single-stranded RNA virus of the genus *Morbillivirus* in the family *Paramyxoviridae* characterized in 1954 by Enders and Peebles with 23 known genotypes. It is spread by droplets or direct contact with nasal or throat secretions of infected persons; less commonly by airborne spread or by articles freshly soiled with secretions of nose and throat. Measles is one of the most readily transmitted communicable diseases and probably the best known and most deadly of all childhood rash/fever illnesses. Measles is characterized by rash, fever, and cough, coryza or conjunctivitis and is transmitted by pharyngeal or nasal secretions, normally from four days before to four days after the onset of rash. The incubation period is normally 10-14 days and the possible complications include otitis media, laryngotracheobronchitis, pneumonia, diarrhea, encephalitis and secondary bacterial infections. Children aged < 5 years who are living in poor conditions or are malnourished, and adults or patients with immune deficiencies have a greater risk of severe complications [6]. Subacute sclerosing panencephalitis (SSPE), a degenerative neurological disease that occurs several years after infection is the most severe condition related to measles infection especially in the very young. The increased risk of developing SSPE after measles virus infection in young children underscores the importance of childhood immunization programs that decrease measles virus transmission and, therefore, reduce the risk of exposure to measles among infants and prevent the devastating disease SSPE [7]. Measles can be effectively prevented by vaccination which provides lifelong immunity to most recipients against all 23 recognized genotypes.

High immunization coverage has dramatically reduced the incidence of measles in Catalonia since measles vaccine was included in vaccination schedule in 1981. Despite overall high vaccination coverage, measles continues to cause frequent outbreaks. However, given the current epidemiological situation [8-12], continued awareness and efforts are needed. Especial efforts should be set concerning mass-gathering events and high travelling frequency among their population as well as from other parts of the world which offer favorable conditions for the spread of the virus between countries.

In Catalonia, a region in the Northeast of Spain with a population of more than 7.5 million inhabitants, autochthonous measles was declared eliminated in the year 2000 [13] as the result of high Measles Mumps Rubella vaccine (MMR) coverage for first and second dose (15 months and 4 years.) since mid 90's, from then on then sporadic imported cases and small outbreaks appeared until August 2006, when a large measles outbreak appeared affecting 381 people, 50% of which were below 15 months of age [14]. From January 2008 first dose administration of MMR was in consequence lowered to 12 months of age. A new honeymoon period went by until at the end of 2010, again, several new importations of different genotypes of wild MV, from neighboring countries triggered another outbreak on November 2010 with a different age distribution sparing small children from infection and striking young adults, mainly adults >25 years.

The aim of this study is to compare differences in age distribution and incidence rates (IR) of cases resulting from first dose MMR vaccine administration changed from 15months to 12months of age and to underscore the importance of enhanced surveillance and implementation of actions to prevent disease and hospitalization for all ages and especially in hard to reach susceptible population.

1. Material and methods

Urgent reported suspected cases of measles to the Public Health Surveillance units were registered and data on age, vaccination status, clinical course and epidemiological information were obtained by case interviews and review of medical records.

Samples for virological confirmation and genotyping of cases were collected as established in the Measles Elimination plan guidelines and delivered to the Microbiology Department of the H Clinic of Barcelona. Serum samples were collected after 3rd day of onset and measles specific antibodies IgG and IgM were determined by an ELISA Assay (Vircell ®). Nasopharyngeal and urine samples were collected and tested by real-time RT-PCR. In accordance with WHO recommendation for molecular epidemiology of measles, phylogenetic analysis of the 450 nucleotides that code for the carboxy-terminal 150 amino acids of the measles nucleoprotein (N) gene was used for genotype determination. Sequences obtained during this study were submitted to Health Protection Agency (HPA) measles database. Statistical assessment of incidence rates (IR) and risk ratios (RR) and their 95%CI, hospitalization rate (HR) by age group were determined. Statistic Chi^2, Fisher's test and statistic z were used for comparing variables and proportions. Statistical analysis was performed by means of the SPSS®

18.0 statistical package for windows (SPSS; Chicago, USA). Statistical significance set at α=0.05.

2. Results

During the study period 489 suspected measles cases were notified to the corresponding regional epidemiological surveillance units versus (vs) 549 in the 2006-2007 outbreak. Total number of confirmed cases was 305 vs 381 in 2006; showing slight statistical difference in confirmation rates (62.4% vs 69.1%) [OR:0.73;95%CI: 0.56-0.95; (p=0.02)]. Difference in global IR showed statistical significance (4.05/100,000 vs 6.6/100,000; (RR: 1.3 95%CI 1.08-1.46). Mean age of cases was 20 yrs in 2010 (SD 14.8 yrs; range 3m-51yrs) vs 15m (SD13.1yrs; range 1m-50yrs) in 2006. Highest proportion of cases was set in ≥ 25 yrs (47.4%) in 2010 vs 24.2% in 2006 (p<0.001). Statistically significant differences were also observed in IR for ≤ 15m (49/100,000 vs 278.2/100,000; (RR: 3,9; 95%CI 2.9-5.4) (Fig. 1) and in HR 29.8% vs 15.7% (OR:2.3;95%CI: 1.54-3.45).

The highest percentage of hospitalized patients occurred in those older than 25yrs was 37.4 % vs 25.0 % in 2006 [OR:1.79;95%CI: 1.01-3.18 (p=0.05)] (Table 1). Eighty percent of hospitalized cases presented complications

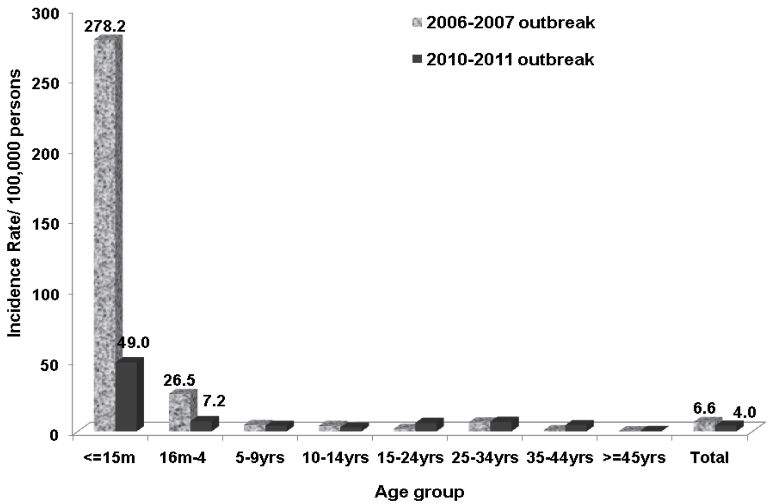

Figure 1. Differences in incidence rates of confirmed measles cases of two outbreaks according to age group. Catalonia 2006-2007 and 2010-2011 outbreaks [15].

Table 1. Differences in hospitalization rates of confirmed measles cases of two outbreaks according to age group. Catalonia, 2006-2007 and 2010-2011 outbreaks [15].

Age group	**Hospitalization rate 2006-2007 outbreak n**	**%**	**Hospitalization rate 2010-2011 outbreak n**	**%**	**OR (95%CI)**	**p**
≤15m /12m*	25/190	13.2%	12/44	27.3%	2.48 (1.14-5.38)	0.04
1-4 yrs	5/66	7.6%	4/35	11.4%	1.57 (0.42-5.85)	0.72**
5-14 yrs	4/23	17.4%	5/27	18.5%	1.07 (0.27-4.29)	1**
15-24 yrs	3/10	30.0%	15/52	28.8%	0.95 (0.23-3.78)	1**
>25 yrs	23/92	25.0%	55/147	37.4%	1.79 (1.01-3.18)	0.05
Total	**60/381**	**15.7%**	**91 /305**	**29.8%**	**2.3 (1.54-3.45)**	**<0.001**

*Below first dose vaccination age ;** Fisher's exact Test

in contrast to 58.3% in the 2006 outbreak, being gastrointestinal symptoms such as diarrhea and vomiting (33%) the most frequent. A higher, although not significant, proportion of pneumonia was observed (23 cases: 26%) when compared to 2006 (8 cases: 13.3%) [OR: 1.90; 95%CI: 0.74-4.96 (p=0.21)].

Laboratory testing was performed in 452 out of 489 suspected cases (92.4%) and of these 262 (58%) were confirmed cases and 190 were classified as non measles cases. Of the 262 laboratory confirmed cases, 238 (90.8%) were positive for MV by real-time RT-PCR, 81 (31%) were positive for IgM measles specific antibodies and 54 (20.6%) cases were both positive for real-time RT-PCR and IgM. Seventy percent of cases were confirmed on basis of positive urine and/or pharyngeal swab positive RT-PCR MV test whereas in the 2006 outbreak this percentage accounted for only 19.7% of laboratory confirmed cases.

Phylogenetic analysis of the minimum recommended 450 nucleotides of N gene of 227/238 (91%) out of all RT-PCR positive samples revealed that the strains belonged to six different genotypes: A (3; 1.6%), B3 (147; 59.5%), D4 (66; 33.2%), D8 (7; 2.8%), D9 (6; 2.4%) and G3 (1; 0.4%) (Fig. 2).

Genotype A was related to vaccine-induced virus infection. Two hundred and seventy one cases /305 (89%) were unvaccinated people of these 36/271 (13.3%) cases were below vaccination age (12 m) and 32 (11.8%) refused vaccination on philosophical beliefs. Twenty six cases (8%) had one dose and 8 (3%) had 2 doses. One of these cases vaccinated with 2 doses of MMR occurred in a physician working at a hospital emergency department. Seventy eight cases were of foreign origin (25.3%) vs 39 (10.2%) in the 2006 outbreak [OR: 2.90; 95%CI: 1.87-4.53 (p<0.001)]; and 11 cases (3.6%) occurred in healthcare settings vs 11(2.9%)in the 2006 outbreak [OR: 1.25; 95%CI: 0.50-3.17 (p=0.75)].

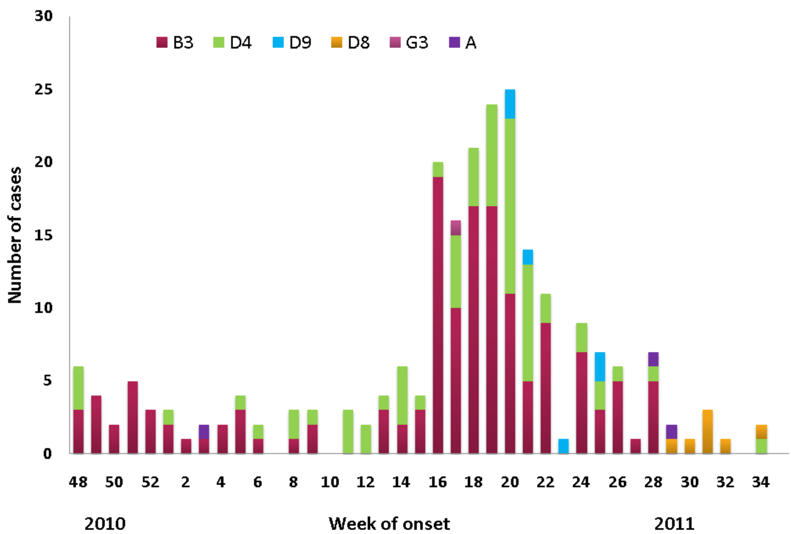

Figure 2. Distribution of genotypes according to week of onset of confirmed cases. Catalonia 2010-2011 outbreak [15].

3. Discussion

The increase in measles cases in 2010 occurred despite a steady rise in regional and global MMR coverage. Measles surveillance data and outbreak investigations provide critical information to identify gaps in population immunity and lead to corrective actions and refinements of vaccination strategies.

Adapting vaccination strategies to the epidemiological scenario is important to control of the disease, thus with the evidence gathered from one large outbreak [14], infants have been spared from measles infection in this second large outbreak four years later when other European countries have had high incidence in infants below vaccination scheduled age [8,16-19]. Surveillance data analyses and outbreak investigations should continue to be used to complement vaccination coverage monitoring to identify gaps in vaccination programs [20]. Yet measles transmission has been firmly re-established in some European Union (EU) Member States to the extent of even exporting measles to the rest of the world, threatening to undermine years of efforts to eliminate endemic transmission of the measles virus [10,21].

The difference in global hospitalization rate (29.8% vs 15.7%) and higher proportion of complications (80% vs 53.7%) could be explained by the higher proportion of adult cases affected in this second outbreak in which the mean age of cases was 20 yrs (SD 14.8 yrs; range 3m-51yrs) vs 15m in the 2006 outbreak [22]. Yet hospitalization rate in infants below vaccination age was still high (27.3% vs 13.2%) compared to the previous and other outbreaks [23]. This could reflect a higher sensitivity and therefore higher degree of hospitalization not solely on severity of disease. Although further studies should explore whether the fact that cases were infected by different genotypes that might also have different severity.

The implementation of molecular diagnostic and genotyping techniques allowed to gathering epidemiological information on measles virus circulating types. Genotypes B3 and D4 were the predominant genotypes in the second measles outbreaks in Catalonia while the first was entirely identified as genotype D4 [24].

Genotypes B3 and D4 showed genetic differences between sequences with a maximum genetic distance of 2 nucleotides in the genomic region studied, revealing different genetic viral variants within the same genetic group. The remaining genotypes D8 and D9 appeared in sporadic cases or related to small limited outbreaks during the study period. Measles genotype G3 is generally associated with measles infections in south-east Asia, or in sporadic cases with links to south-east Asia [25]. There had been no reported cases of measles G3 in Europe since 2006 until by the end of 2010 it reappeared in several different countries in Europe [26]. Unlike other outbreaks [14,16,27] six different genotypes have been isolated in Catalonia during the study period, showing several importations as a result of the high incidence in other neighboring territories.

The high proportion of cases in immigrant population (24.9%) reflects the fact that, although immigrants are offered the same health care services as the indigenous population, the rate of MMR vaccination coverage is lower in this population [28]. In the 2006 outbreak, this proportion was significantly lower (10.2%) probably because immigrant parents do adhere to pediatric vaccination schedules in a greater proportion than adults. This fact stresses the need to offer complete adult vaccination schedule to this population when consulting primary care services.

Although nosocomial infection has been described as an important source for measles infection [19,29], in this, as in the previous outbreak, only 11 cases (3.6% and 2.9% respectively) were related to healthcare workers with few secondary cases arising from them, this fact underscores the importance of maintaining high MMR immunization coverage and of the efforts addressed to improve this coverage in order to reach zero cases in healthcare workers in future outbreaks.

First cases identified in this 2010-2011 outbreak occurred within a setting of unvaccinated children due to philosophical reasons (11.8%) giving place to transmission in an area where anti-vaccine movement is active. This was not so in the previous outbreak where rejection of vaccination for philosophical reasons (1.5%) would not have greatly influenced maintained transmission of chains [14]. Parents who refuse to vaccinate their children are an important issue because of the influence it can have on sustaining transmission after an importation of MV within a community. Several authors have studied this phenomenon to find out which are the keys to this belief [30,31]. The anti-vaccine movement represents ongoing groups who share concerns based on misconceptions, unfortunately, they not only put their own children at higher risk for disease but they also contribute to the failure of communities to achieve protective vaccination rates and to herd immunity failure even among highly vaccinated populations [32].

The fact that a physician correctly vaccinated with 2 doses of MMR became ill has also been observed by other authors [33]. It might indicate that in an outbreak setting with persistent close contact with MV, waning of immunity over time is another issue to be followed up closely, especially in regions where circulation of wild MV is low and could pose the possibility of recommending a booster dose for healthcare workers in an outbreak setting [34,35].

Since the interruption of endemic measles transmission in December of 2000 and in spite of the high-immunization coverage, measles outbreaks and sporadic infections have occurred in Catalonia due to importations of measles, yet no sustained transmission had occurred and outbreaks, to the exception of those described in this study, were quickly set under control. Surveillance data and results of molecular epidemiology indicate that there is a continuous exposure to MV from other regions of Europe and of the world. The co-circulation of different genotypes and several viral variants for genotypes B3 and D4 revealed that 2010-2011 outbreak was caused by multiple imports from abroad or other Spanish regions (Andalusia, Madrid) and confirms the absence of endemic infection. The change of the month of administration of the first dose proved successful in preventing disease and hospitalization in unvaccinated infants, but young adult population are far harder to reach than children. In this pouch of susceptible, achieving high coverage is difficult and furthermore they are the most mobile population, greatly prone to travel and be a source for importation themselves.

4. Conclusion

Elimination and eradication programs are laudable goals, but they carry with them an awesome responsibility. There is no room for failure. Careful and deliberate evaluation is a prerequisite before embarking on any program. Elimination and eradication are the ultimate goals of public health. The only question is whether these goals are to be achieved in the present or some future generation.

In conclusion, given the current epidemiological situation, continued awareness and efforts to reach young adult population (especially healthcare workers and travelers) are needed to stop the spread of the virus. Enhanced measles surveillance is critical to disease control by early identification of measles cases and thus allowing for early detection and control of outbreaks, assessing on-going transmission patterns in order to mount more effective vaccination measures.

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