Research

Measles: effect of a two-dose vaccination programme in Catalonia, Spain

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The study reports incidences of measles in Catalonia, Spain, as detected by surveillance, and analyses the specific characteristics of the outbreaks reported for the period 1986–95. Incidences per 100 000 inhabitants were calculated for the period 1971–95. The following variables were studied: year of presentation, number of cases, median age, transmission setting, cases with a record of vaccination and preventable cases. Associations between variables were determined using odds ratios (OR). The incidence of measles declined from 306.3 cases in 1971 to 30.9 in 1995. A total of 50 outbreaks were investigated. The outbreaks that occurred in the last two years of the study had a higher likelihood of having a transmission setting other than primary school (OR = 3.9); a median case age > 10 years (OR = 7.2); and fewer than 6 cases (OR = 2.3). The characteristics of recent outbreaks, marked by a rise both in transmission outside the primary-school setting and in median age, indicate the need for the introduction of a specific vaccination programme at the end of adolescence in addition to control of school-related outbreaks.

Voir page 136 le résumé en français. En la página 136 figura un resumen en español.

Introduction

Throughout history, measles has occasioned high mortality and morbidity. Nowadays, despite being a preventable disease, it still gives rise to 45 million cases and over one million deaths worldwide each year (*1, 2*).

The availability of an attenuated vaccine of proven high efficacy (90–95%), the markedly stable nature of the virus, the nonexistence of carriers, and the fact that humans constitute the sole disease reservoir (*3, 4*), led to the proposal that measles could be eliminated from extensive geographical areas. Hence, within the context of the strategy of "Health for all by the year 2000", the European Region of WHO proposed that measles should be eliminated from all countries in the region by the year 2000.

Subsequently, however, epidemiological data have indicated that in developed countries, even with vaccine coverage approaching 100%, sporadic cases and epidemic outbreaks of measles could continue to appear (*5, 6*), owing to the difficulty of achieving sufficient herd immunity to eliminate a disease whose level of airborne communicability is far higher than had been supposed. In 1991 the European Region of WHO therefore set a new target: that by the year 2000 the incidence of measles in all Member States in the region would be less than 1 per 100 000 inhabitants. More recently it has been recommended that the date for elimination should be set between 2005 and 2010 (*7*). Diverse strategies have been proposed to control the disease and its subsequent eradication (*3, 4, 8*). It is absolutely essential, however, that region-specific measles epidemiology should be ascertained so that the methods best adapted to the respective characteristics of each location can be applied (*9, 10*).

In Catalonia (population 6 million), an autonomous region situated in north-east Spain, a systematic immunization programme was introduced in 1981, based on the administration of a single dose of measles vaccine at the age of 12 months. Since 1988, two doses of vaccines have been administered: the first at 15 months, and the second at 11 years. On the basis of the number of doses of vaccine distributed to vaccination centres, it is estimated that vaccination coverage for cohorts born after 1981 is in excess of 95%. In 1991 a health plan was drawn up which aimed among other things at eliminating indigenous measles by the year 2000 and reducing the disease incidence to less than 10 per 100 000 by 1995. Nevertheless, and bearing in mind that surveillance was incomplete, the lowest incidence for the entire period (10.6 per 100 000 inhabitants) occurred in 1993, with no epidemic outbreak of measles being detected. In 1994 and especially in 1995 there was a rise in the incidence and the number of reported outbreaks.

The present study sought to assess the measles elimination strategy in Catalonia by examining incidence trends over the last 25 years and analysing the specific characteristics of the outbreaks registered in the period 1986–95.

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Materials and methods

Historically, records of notifiable diseases in Spain have been based on the number of cases reported by local public health authorities. In January 1982, a directive came into force in Catalonia which reformed the disease notification procedure. Under the terms of this directive, in addition to local public health authorities, the heads of health care centres (in- and outpatient) were also required to return a form showing the number of diseases diagnosed by all physicians in their centres. Among the diseases to be reported by this procedure was measles, which, along with the others, was to be reported on a clinically suspect case basis, as determined by the physician's criteria.

It was subsequently recommended that the following clinical case definition of measles be used for reporting purposes: a disease displaying the following characteristics: a) generalized maculopapular rash; b) fever >38.3 °C; and c) cough, rhinitis or conjunctivitis. Preventable cases were deemed to be those that had not been vaccinated in accordance with the vaccination schedule, in the absence of any medical contraindications or objections to vaccination of a religious and/or philosophical nature.

The measles time–trend study was based on year-by-year aggregation of weekly reports received by the Department of Public Health and Social Security for the period January 1971 to December 1995. For rate calculation purposes, the 1971, 1981 and 1991 official census population plus the intercensus population calculated by the National Statistic Office (*Instituto Nacional de Estadistica*) were used. The trend in the incidence over time was studied using Pearson's correlation coefficient *r*.

There is a statutory duty in Catalonia to report epidemic outbreaks to the Provincial Public Health and Social Security Authorities. Once investigation and adoption of the relevant lines of action have been completed, the technical staff must then draw up a health status report and forward it to the Department of Public Health and Social Security. To study such outbreaks, we reviewed all reports on measles outbreaks that had been sent to the General Directorate of Public Health since 1986 (the year when for the first time since 1982 measles outbreaks were reported and studied in Catalonia). A measles outbreak was defined as the association of two or more cases within a maximum period of 18 days. The variables studied were as follows: year of presentation (divided into three periods: 1986–87, 1988–93 and 1994–95); reporting delay in days; existence of serologically confirmed cases; number of cases; median age; transmission setting; number of cases with a record of vaccination; and number of preventable cases. Association of the dependent variable (year of presentation) with the remaining variable of the study was determined using the odds ratio (OR), with a 95% confidence interval (CI). Data were analysed using the Epi Info 6.04 software package.

Results

The incidence of measles per 100 000 inhabitants, as registered by the epidemiological surveillance system,

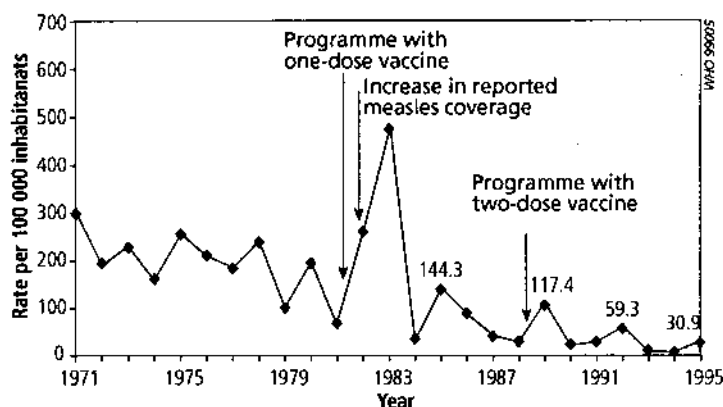Fig. 1. **Trend in the incidence of measles in Catalonia, 1971–95**

Table 1. **Number of notified cases of measles and investigated outbreaks of measles in Catalonia, 1986–95**

Year	No. of notified cases of measles	Rate per 100 000 inhabitants	No. of cases in outbreaks	No. of outbreaks
1986	5 489	92.2	21 (0.4)[a]	1 (2.0)
1987	2 612	43.6	21 (0.8)	2 (4.0)
1988	1 869	31.7	3 (0.2)	1 (2.0)
1989	7 022	117.4	42 (0.6)	1 (2.0)
1990	1 242	20.7	171 (13.8)	3 (6.0)
1991	1 821	30.4	62 (3.4)	4 (8.0)
1992	3 596	59.3	182 (5.1)	10 (20.0)
1993	645	10.6	0 (0.0)	0 (0.0)
1994	453	7.5	43 (9.5)	5 (10.0)
1995	1 838	30.9	137 (7.4)	23 (46.0)
Total	**26 587**		**682 (2.6)**	**50 (100.0)**

[a] Figures in parentheses are percentages.

declined from 306.30 cases in 1971 to 30.9 in 1995 (Fig. 1). The incidence fell over this period by 89.9%, yielding a statistically significant ($P = 0.001$) Pearson correlation coefficient $r = -0.67$. From 1971 to 1981 there were important outbreaks every two years. Subsequently, despite an increase in the number of reporting centres, a marked decrease in incidence was observed in association with the establishment of the vaccination programme (Fig. 1). It should be noted that, following the sharp decline in 1983, incidences nevertheless increased in subsequent years, i.e. 1985 (144.3 per 100 000), 1989 (117.4), 1992 (59.3), and 1995 (30.9).

In all, 50 outbreaks, with a total of 682 cases, were investigated. The number of outbreaks per year varied from none at all in 1993 to 23 in 1995. The proportion of cases of measles involved in outbreaks with respect to the number of numerically notified cases varied from 0% (in 1993) to 13.8% (in 1990) (Table 1). Outbreaks were notified to the epidemiological surveillance system with a median reporting delay of 15 days (range: 1–72); and the median number of cases per outbreak was 6 (range: 2–95).

In 20% of outbreaks (10/50) there were serologically confirmed cases. Statistically significant differences in median age of cases, primary-school transmission, number of cases and proportion of vaccinated cases were not observed between laboratory-confirmed outbreaks and those with only epidemiological confirmation (Table 2).

The most frequent transmission settings were as follows: primary school (50%), family (18%), community (12%), secondary school (8%), nursery school (4%), armed forces (3%), and hospital (2%). One or more cases were hospitalized in 11 outbreaks (22.0%) and overall, 4.1% of all cases were admitted to hospital. An important proportion of cases (44.9% (245/545)) had been vaccinated (Table 3), 0.9% (5/545) with two doses and 44.0% (240/545) with a single dose; only 27.8% (148/532) were preventable.

The median age of measles cases in 45.8% of outbreaks was 6–10 years, and in 18.7%, 16–20 years. The median age for the remaining outbreaks was distributed in a lower proportion among the other age groups. A shift to the older groups was observed with time. For the 0–5-year group, 83.3% of the outbreaks occurred in 1988–93, while for people aged ⩾ 15 years all the outbreaks occurred in 1994–95 (Table 4).

The outbreaks in the last two years of the study (1994 and 1995) had a higher likelihood of having the following: a transmission setting other than primary school (OR = 3.9, 95% CI = 1.0–16.4); a median age above 10 years (OR = 7.2, 95% CI = 1.4–41.2); and fewer than 6 cases per outbreak (OR = 2.3, 95% CI = 0.6–9.3) (Table 5).

Discussion

Following introduction of the vaccination programme, measles incidences in Catalonia declined markedly (89.9%), akin to that witnessed by other countries (4, 11). However, after an initial drop in the incidence (5, 11, 12), important epidemics took place in 1985, 1989, 1992 and 1995, although in no instance reaching the levels registered prior to the introduction of the vaccination programme.

Table 2. **Specific characteristics of outbreaks of measles with and without serological confirmation in Catalonia, 1986–95**

Variable	Serological confirmation: Yes	No	Odds ratio
Median age (years)			
0–10	4 (40.0)[a]	14 (40.0)	Reference
>10	6 (60.0)	24 (60.0)	0.9; *0.2–4.5*[b]
Primary-school transmission			
Yes	4 (40.0)	21 (52.5)	Reference
No	6 (60.0)	19 (47.5)	1.7; *0.3–8.5*
No. of cases			
>6	6 (60.0)	19 (47.5)	Reference
2–6	4 (40.0)	21 (52.5)	0.6; *0.1–3.0*
% vaccinated			
0–30	6 (60.0)	10 (26.3)	Reference
31–60	1 (10.0)	16 (42.1)	0.1; *0.0–1.1*
61–100	4 (30.0)	12 (31.6)	0.4; *0.1–2.7*

[a] Figures in parentheses are percentages.
[b] Figures in italics are 95% confidence intervals.

Table 3. **Distribution of cases with record of vaccination and preventable cases in reported outbreaks in Catalonia, 1986–95**

Variable	No. of cases[a]
Vaccinated	
Yes	245 (44.9)[b]
1 dose	240 (44.0)
2 doses	5 (0.9)
No	300 (55.1)
Preventable	
Yes	148 (27.8)
No	384 (72.1)

[a] Excluding cases without data for the variable shown.
[b] Figures in parentheses are percentages.

Table 4: **Distribution of outbreaks of measles in Catalonia, by median age of cases, 1986–95**

Median age[a] (years)	Period 1986–1987 n	1988–1993 n	1944–1995 n	Total
0–5	0 (0.0)[b]	5 (83.3)	1 (16.7)	6
6–10	3 (13.6)	9 (40.9)	10 (45.4)	22
11–15	0 (0.0)	3 (50.0)	3 (50.0)	6
16–20	0 (0.0)	0 (0.0)	9 (100.0)	9
>20	0 (0.0)	0 (0.0)	5 (100.0)	5
Total	**3**	**17**	**28**	**48**

[a] Data were not reported in two outbreaks.
[b] Figures in parentheses are percentages.

An increase in cases, especially in the form of outbreaks, often affecting a high proportion of the vaccinated population, has been observed in a number of countries after such initial periods of apparent control (3, 4, 11–13). Among the reasons that can be adduced to explain such outbreaks, the following warrant special mention (3, 14, 15): a) the highly contagious nature of measles, surpassing that estimated in the mathematical models used; b) primary (14, 16) and secondary (16, 17) vaccine failures; c) defects in vaccination programmes, with different proportions of children without access to vaccines (11); and d) other aspects, such as the role of already immune persons or asymptomatic cases in transmission — among the vaccinated population in particular — could also play an important part in the evolution of epidemic outbreaks (5, 14).

The study's main limitation is the lack of information on the validity of measles reporting in Catalonia. Only the outbreaks that were reported and investigated were analysed. Outbreaks are under-registered compared with the numerically reported cases. Moreover, only 20% of outbreaks were serologically confirmed. Although the clinical profile of measles has traditionally been considered very characteristic, a number of studies have shown that the positive predictive value of measles reporting may be very low, particularly in countries in which incidence declines and there is an appreciable proportion of cases with a record of having been vaccinated (9, 10, 18). In any outbreak, a reporting delay, in addition to adversely affecting the validity of the data, limits the efficacy of any control measures adopted (19, 20). It has been stressed that availability of quick, straightforward analytical techniques, such as salivary diagnosis, would facilitate both epidemiological surveillance of the disease and swift introduction of control measures (4, 21–24).

The median age of cases in 45.8% of outbreaks was 6–10 years, and in 18.7%, 16–20 years, suggesting that, as indicated in other studies (4, 21), the age of cases tends to be much older than those reported prior to vaccination; a shift of the outbreaks to the older age groups is observed. In Catalonia, the 5–10-year age group will have contained some cohorts that were vaccinated at age 12 months, which probably entailed a higher proportion of primary vaccine failures (6, 16). The 16–20-year age group will have comprised cohorts with lower vaccine coverage and a lower opportunity to develop natural immunization because of lower circulation of the virus. It has already been observed that this age segment is a risk group for measles (6, 25).

In agreement with other studies (11, 25), the most frequent transmission settings proved to be primary schools and households. In recent years, a lower yet highly significant proportion of cases has been registered in secondary schools (age ≥15 years) and in the armed forces. Health care centres have been repeatedly described as a risk

Table 5. Specific characteristics of outbreaks of measles in Catalonia, 1986–95

Variable	Period		
	1986–87	1988–93	1994-95
Median age (years)			
0–10	3 (100.0)[a]	14 (82.3)	11 (39.3)
>10	0 (0.0)	3 (17.6)	17 (60.7)
Odds ratio	0; *0.0–19.6*[b]	Reference	7.2; *1.4–41.2*
Primary-school transmission			
Yes	2 (66.7)	13 (68.4)	10 (35.7)
No	1 (33.7)	6 (31.6)	18 (64.3)
Odds ratio	0; *0.0–19.6*	Reference	3.9; *1.0–16.4*
No. of cases			
>6	2 (66.7)	10 (52.6)	9 (32.1)
2–6	1 (33.7)	9 (47.4)	19 (67.8)
Odds ratio	0.6; *0.1–10.4*	Reference	2.3; *0.6–9.3*

[a] Figures in parentheses are percentages.
[b] Figures in italics are 95% confidence intervals.

setting for measles transmission, and this should be borne in mind in outbreak control (26, 27).

An important proportion of cases (44.9%) had been vaccinated. This is comparable to that found in other studies and congruent with an acceptable vaccine coverage (28, 29). In countries that increase measles vaccination coverage, the proportion of cases with a record of vaccination also increases. Only five cases had a previous history of two doses of vaccine and these represent the infrequent primary vaccine failures that do not seroconvert (30).

Measles epidemiology underscores the soundness of the 1988 decision to incorporate a second dose of vaccine, though this too should perhaps be boosted by some complementary measure. Among the cases with a record of vaccination, 97.8% had received a single dose of vaccine; in addition, 45.8% of the outbreaks occurred in the 5–10-year age group. These findings indicate that administration of the second dose of measles–mumps–rubella (MMR) combined vaccine at age 4–6 years (before starting school) instead of at 11 years of age could prevent an important proportion of outbreaks in Catalonia. Also, the recent increase of transmission among adolescents and young adults indicates that existing strategies should be supplemented by control of immunization status at the end of adolescence (3, 4, 23, 31, 32), on termination of secondary school, or on entrance to university, the labour market or the military (31).

Other countries have administered this second dose of vaccine using the catch-up strategy (3, 4, 7, 17, 23), inoculating all persons aged 1–14 years, irrespective of their vaccine or disease case histories, thereby achieving temporary elimination of measles virus. Certain aspects of this strategy still remain to be elucidated, however, such as how campaigns should be scheduled and which age groups should be covered (13).

In order to achieve elimination of measles before the year 2000, the dual strategies of catch-up vaccination of some cohorts of students (probably aged 7–18 years) and bringing forward the second dose to age 4–6 years should be considered. Both strategies will reduce the number of susceptible individuals in those age groups that appear to be more susceptible for measles transmission. In view of the organizational requirements and economic burden of such a strategy, it is probably only feasible if it is coordinated with other European countries and with the specific aim of eliminating the disease in the region (*33*).

As for all diseases in the process of being eliminated, it is essential to establish an epidemiological surveillance system that allows confirmation of each reported case, characterization of the virus involved using molecular epidemiology and detailed study of each outbreak (*7, 25, 28, 33*). Such information is essential in order to reorientate the strategies of vaccination programmes and to certify the eventual elimination of disease in a particular area (*7, 25, 33*). ∎

Résumé

Rougeole : effet d'un schéma de vaccination à deux doses en Catalogne (Espagne)

La Catalogne (Espagne) s'est donné pour but d'éliminer la rougeole autochtone d'ici l'an 2000; toutefois, malgré une couverture vaccinale acceptable, le nombre de flambées s'est accru ces derniers temps. L'article donne les chiffres d'incidence fournis par le système de surveillance et analyse les caractéristiques propres des flambées signalées au cours de la période 1986-1995.

Les auteurs ont calculé l'incidence de la rougeole pour 100 000 habitants au cours de la période 1971-1995. Ils ont défini une flambée de rougeole comme l'association de deux cas ou davantage et étudié les variables suivantes : année de présentation, nombre de cas, âge médian des cas, lieu de transmission, cas ayant des antécédents de vaccination et cas évitables. Pour déterminer l'association de la variable dépendante avec les autres tableaux de l'étude, on a utilisé l'*odds ratio* (OR) et un intervalle de confiance (IC) de 95%.

L'incidence pour 100 000 habitants mesurée par le système de surveillance est tombée de 306,3 cas en 1971 à 30,9 cas en 1995. Au total, 50 flambées totalisant 682 cas ont été étudiées. Le nombre médian de cas par flambée était de 6 (valeurs limites : 2-95). L'âge moyen des cas était de 6-10 ans dans 45,8% des flambées et de 16-20 ans dans 18,7% des autres. Les lieux de transmission les plus fréquents étaient les suivants : écoles primaires (50%) et ménages (18%). Dans une proportion importante (44,9%) les cas avaient été vaccinés et seuls 27,8% d'entre eux se sont révélés être évitables. Les flambées des deux dernières années de l'étude (1994 et 1995) avaient une plus grande probabilité de correspondre à des situations du type suivant : lieu de transmission autre qu'une école primaire (OR=3,9; IC à 95%=1,0-16,4); âge médian des cas >10 ans (OR=7,2; IC à 95 % =1,4-41,2); effectif inférieur à 6 cas (OR=2,3; IC à 95 %= 0,6-9,3).

Les caractéristiques des récentes flambées de rougeole survenues en Catalogne, marquées par une augmentation de lieux de transmission autres que les écoles primaires et de l'âge médian des cas, soulignent la nécessité de mettre en place un programme spécifique de vaccination à la fin de l'adolescence, en plus de la lutte contre les foyers de rougeole en milieu scolaire. L'introduction d'un système de contrôle des dossiers individuels de vaccination à la fin des études secondaires ou encore à l'entrée à l'université ou lors du service militaire, pourrait contribuer à faire reculer le nombre de ces flambées.

Resumen

Sarampión: efecto de una pauta de vacunación con dos dosis en Cataluña (España)

Se ha fijado la meta de eliminar el sarampión indígena en Cataluña (España) para el año 2000; sin embargo, pese a haberse alcanzado una cobertura aceptable de vacunación, recientemente se ha detectado un aumento del número de brotes. En el presente estudio se da cuenta de las incidencias detectadas por el sistema de vigilancia y se analizan las características específicas de los brotes notificados durante el periodo 1986-1995.

Se calcularon las cifras de incidencia de sarampión por 100 000 habitantes correspondientes al periodo 1971-1995. Se calificó de brote toda asociación de dos o más casos, y se estudiaron las siguientes variables: año de presentación, número de casos, edad mediana de los casos, entorno de transmisión, casos con registro de vacunación y casos prevenibles. La asociación entre la variable dependiente (año de presentación) y los datos de las restantes tablas del estudio se determinó mediante la razón de posibilidades («odds ratio», OR), con un intervalo de confianza (IC) del 95%.

La incidencia de sarampión por 100 000 habitantes detectada por el sistema de vigilancia disminuyó de 306,3 casos en 1971 a 30,9 en 1995. Se investigaron en total 50 brotes, que sumaron 682 casos. La mediana de casos por brote fue de 6 (intervalo: 2-95). La edad mediana de los casos fue de 6-10 años en el 45,8% de los brotes, y de 16-20 años

en el 18,7%. Los entornos de transmisión más frecuentes fueron la escuela primaria (50%) y el hogar (18%). Una importante proporción de los afectados (44,9%) había sido vacunado, y sólo un 27,8% de los casos era prevenible. En los brotes declarados en los dos últimos años del estudio (1994 y 1995) concurría con mayor probabilidad alguna de las siguientes circunstancias: un entorno de transmisión distinto de la escuela primaria (OR = 3,9, IC 95% = 1,0-16,4); una edad mediana de los casos >10 años (OR = 7,2, IC 95% = 1,4-41,2); y menos de 6 casos (OR = 2,3, IC 95% = 0,6-9,3).

Las peculiaridades de los brotes observados recientemente en Cataluña, caracterizados por un aumento de la transmisión en entornos distintos de la escuela primaria y por un incremento de la edad mediana, indican que es necesario aplicar un programa de vacunación específico al término de la adolescencia como elemento adicional de la lucha contra los brotes escolares. La implantación de sistemas de control destinados a vigilar la situación inmunitaria de los jóvenes al acabar la escuela secundaria o al iniciar los estudios universitarios o el servicio militar podría contribuir al control de esos brotes.

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