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Seroepidemiological evaluation of 1989–91 mass vaccination campaigns against measles, in Italy

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SUMMARY

In 1989–91 anti-measles vaccination campaigns were conducted in several Italian regions to vaccinate all children aged between 13 months and 10–12 years without a history of measles or measles vaccination. This study was conducted to evaluate serological status after the mass vaccination campaigns. In 1994, capillary blood samples were collected from randomly selected children, aged 2–14 years, living in 13 local health units. Antibody titres were determined by ELISA. Blood spot samples were analysed for 4114 (75·6%) of 5440 selected children. Among the 835 that reported measles before 1990, 806 (96·5%) were immune and of the 2798 vaccinated, 2665 (95·2%) were immune. The Edmoston–Zagreb (E–Z) strain vaccine was associated with a lower level of immunity than the Schwarz (SW) strain. A history of measles identified almost all immune children. Vaccination with the SW strain conferred persistent immunity (at least 5 years) in 98% of vaccinees. The strategy was able to unite natural and induced immunity.

INTRODUCTION

Vaccination against measles has been recommended in Italy since 1979, but its widespread use began in 1989. Measles epidemics occurred in 1981, 1984, 1985 and 1988. On average, in the period 1980–9, 49000 cases were reported annually: 86000 per year in the epidemic years and 22000 per year in the interepidemic years. The average incidence rate was 0·81 per 1000 per year, ranging from 0·39 to 1·36 [1]. About 75% of notified cases were in children aged less than 10 years.

Seroepidemiological investigations [2] enabled the level of underreporting and the median age at natural infection to be estimated by geographical area. In Italy as a whole one tenth of the actual measles cases were estimated to be notified, but this ranged from 3% in the South of Italy to 30% in the North. In Southern Italy 50% of children achieved natural immunity by 36 months but in Northern Italy this level was not achieved until 5–6 years. Overcrowding and larger family size were associated with earlier median age of infection in the South of Italy.

Pilot mass vaccination campaigns conducted since 1980 showed that active offer of the vaccination by public health services, targeted at children aged 13 months to 8–12 years, could interrupt circulation of measles. Interruption should persist if almost all children born subsequent were vaccinated in the second year of life [3]. The high positive predictive value of a history of measles [2, 3] means that these children could be excluded from the active offer of vaccination.

SW and E–Z strain vaccines have been available since 1979 and 1989, respectively and their com-

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bination with Urabe 9 (SW) or Rubini mumps strains (E–Z) and the Wistar RA 27/3 rubella strain, since the second half of 1990.

Mass vaccination campaigns were implemented in several local health units in 15 of the 20 Italian regions. Vaccine coverage ranged from 50 to 99% of the target population, depending on how actively measles vaccine was promoted. [4]. As a result, in 1994 only 34% of measles notifications were in children aged less than 10 years [1]. Measles notifications (per 1000 population) decreased in 1990–4, compared to 1980–9 from 4·47 to 1·91 (−57·3%), 5·55 to 2·50 (−55·0%) and 1·64 to 1·39 (−15·2%) in the age groups 0–4, 5–9 and 10–14 years. The total population percentage decrease was −49·4% (from 0·81 to 0·41) [1].

In the first 6 months of 1994 a serological investigation of children, from a sample of local health units that had participated in the mass vaccination campaign, was conducted to evaluate the level of immunity reached in the target population. The aim of this investigation was to confirm the validity of a history of measles as an identifier of immune children, and to evaluate the persistence of immunity induced by the two vaccine strains.

METHODS

A sample of local health units was taken from those that had implemented mass vaccination campaigns in the years 1988–91. The sample was not random but designed to include different levels of implementation.

Group A: Ten out of 41 local health units of Emilia Romagna. In this region mass vaccination campaigns were implemented successfully everywhere (vaccine coverage ranged from 80 to 90%) and residual circulation of measles was mainly in age groups older than 12 years.

Group B: Two local health units, one from Puglia and one from Campania. In these regions less than 50% of local health units implemented mass vaccination campaigns but in those chosen for the investigation vaccine coverage was over 95% and the circulation of indigenous measles has been interrupted since 1990.

Group C: One local health unit (from Basilicata), where vaccine coverage was about 50% and only reduced circulation of measles has occurred.

Parents completed a questionnaire on age, sex and residence of the child, mother's and father's educational level, and measles history and/or vaccination status. Details on the dates of disease or vaccination, who diagnosed measles and who gave vaccine were requested. History of vaccination reported by parents was checked against vaccination registers. After obtaining the written consent of parents, capillary blood samples were collected from children aged 2–14 years randomly selected by systematic or proportional sampling from residence and/or school registers.

In groups A and C only five age groups were included in the investigation. To ensure that the sampling error should not (probability 95%) exceed 10% of the estimated proportion immune in each age group and, considering the availability of local health units, 70, 120, and 100 children from each age group were samples in groups A, B and C, respectively.

Blood spot samples were processed and ELISA performed according the method of Novello and colleagues [5]; the threshold level for positivity was assumed to be 130 mIU/ml.

Comparisons between groups were performed by Student's t or ANOVA (antibody titres expressed as log mIU/ml) and χ^2 (percent of positive) tests. Logistic regression was used to estimate the risk of susceptibility.

RESULTS

Table 1 shows the data on target populations, sample size and response rate for each area group. Out of 5440 selected children questionnaires were completed for 4528 (83·2%) and capillary blood samples obtained from 4114 (75·6%). The educational level of parents completing the interview but refusing the blood test was higher than that of those who consented; no difference in reported immunity status was observed between those who submitted capillary blood samples and those who did not.

Most of the questionnaire non-responders could not be found at the time of investigation, so it was difficult to collect data to characterize them.

Figure 1 shows the percentage of seroimmune children by year of birth and by area group. The percentage of immune subjects in groups A and C increased from 85·3 and 70·6% for those born in the years 1988–9 to 89·3 and 96·9% for those born before 1982. In group B, percentage immunity was higher than 93% in all age groups, ranging from 93·3% in those born in the years 1986–7 to 99·1% in those born in the years 1982–3.

Table 2 shows serological results by history of measles or measles vaccination and by year of birth.

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Table 1. *Target population, sample size and response rate* (%)

Group	Target population	Sample size	Collection of	
			Questionnaires	Capillary blood samples
A (Emilia Romagna)	72044	3500	2900 (82·8)	2515 (71·9)
B (Galatina & Atripalda)	11586	1440	1138 (79·0)	1129 (78·4)
C (Villa d'Agri)	5470	500	490 (98·0)	470 (94·0)
Total	89100	5440	4528 (83·2)	4114 (75·6)

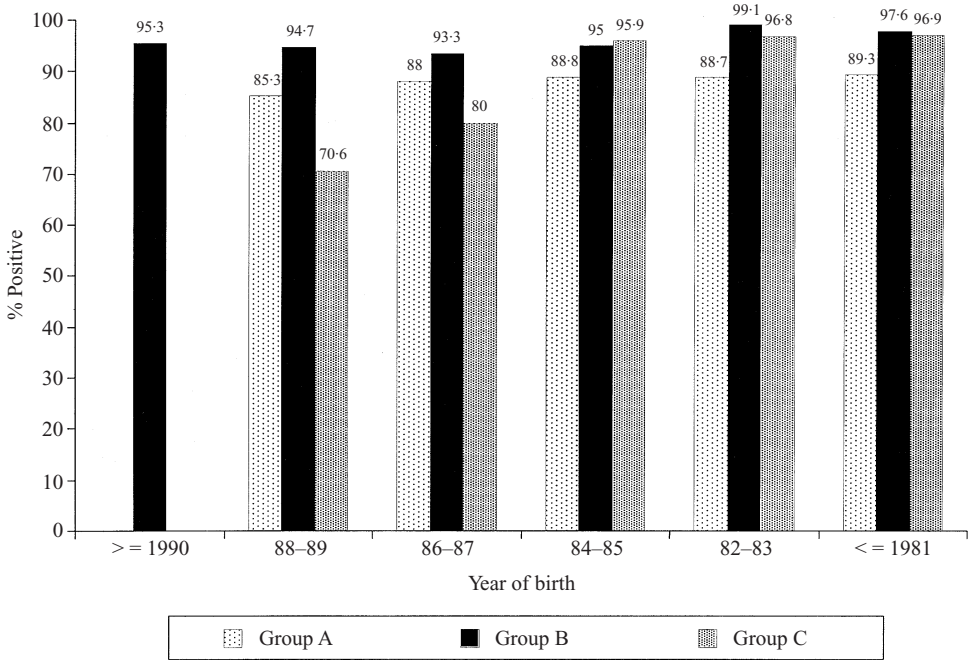

Fig. 1. Serological profile in the groups A, B and C.

For 20 children, information on immunity history was missing; for 35 with history of measles, date of disease was missing too. Of those that reported having had measles before 1990, 806 (96·5%) of 835 were immune, and in the period 1990–3 80 (87·0%) of 92 were immune (OR 4·2, 95% 1·9–8·9). For those vaccinated with SW and E–Z strain, 2190 (97·6%) of 2244 and 475 (85·7%) of 554 were immune (OR 6·8, 95% CI 4·6–9·8). Of 334 children without a history of measles or measles vaccination, 110 (32·9%) were immune, ranging from 53·9% in those born in 1981 to 20·3% in those born in 1988–9 (χ^2 for trend, $P < 0{\cdot}01$). Log GMT values were 3·83 in seropositive subjects with a history of measles before 1990, and 3·85 for a history after 1990. The log GMT values were 3·22 and 2·81 for children vaccinated with SW and E–Z respectively and 3·53 for those without a history of natural or induced immunity.

Figure 2 shows the distribution of seropositive children by antibody titre and by history of measles or measles vaccination. Among seroimmune children vaccinated with E–Z strain, 29·2% had antibody titres equal to or higher than 3·0 Log mIU/ml and 7·9% were higher than or equal to 3·5 compared to 73·9 and 22·7% after SW vaccination. Among seroimmune subjects with a history of measles before 1990, 98·6% had antibody titres higher than 3·0 and 91·2% higher than 3·5 compared to 98·8 and 92·5% for children with a history of measles since 1990.

Table 3 reports the number of subjects, percentage positive and log GMT values by history of measles or vaccination and by area group. The percentage of children in groups A and B without a history of measles or vaccination, who were immune was significantly less than that in group C (22·5, 24·2 and 57·7%, $P < 0{\cdot}01$). The percentage of children in group

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Table 2. *Number of subjects, percentage positive and log GMT values by year of birth and history of measles or measles vaccination. Total sample*

Condition	Serological results	Year of birth						
		⩽ 1981	1982–3	1984–5	1986–7	1988–9	⩾ 1990	Total
No history of measles/ vaccination	*n*	76	53	65	64	69	7	334
	% Pos. (CI)	54 (43–65)	38 (25–53)	28 (17–41)	27 (16–40)	20 (11–32)	0 (0–41)	33 (28–38)
	log GMT (CI)	3·46 (3·30–3·62)	3·71 (3·57–3·85)	3·53 (3·26–3·80)	3·60 (3·36–3·84)	3·35 (3·11–3·60)		3·53 (3·43–3·62)
History of measles < 1990	*n*	290	281	165	82	17	0	835
	% Pos. (CI)	96 (94–98)	98 (95–100)	97 (93–100)	98 (91–100)	71 (44–91)	—	97 (95–98)
	log GMT (CI)	3·80 (3·77–3·83)	3·83 (3·80–3·86)	3·85 (3·81–3·89)	3·87 (3·82–3·93)	3·92 (3·79–4·06)	—	3·83 (3·81–3·85)
History of measles ⩾ 1990	*n*	8	18	20	26	20	0	92
	% Pos. (CI)	88 (84–91)	94 (72–100)	90 (68–99)	81 (60–94)	85 (62–97)	—	87 (78–94)
	log GMT (CI)	3·78 (3·61–3·94)	3·78 (3·64–3·92)	3·78 (3·60–3·96)	3·90 (3·80–4·0)	3·97 (3·9–4·04)	—	3·85 (3·79–3·91)
History of SW vaccination	*n*	309	430	448	508	392	157	2244
	% Pos. (CI)	97 (94–99)	97 (94–99)	99 (97–100)	97 (95–99)	98 (96–100)	98 (94–100)	98 (97–98)
	log GMT (CI)	3·18 (3·14–3·22)	3·19 (3·16–3·23)	3·17 (3·14–3·21)	3·24 (3·20–3·27)	3·27 (3·24–3·31)	3·38 (3·32–3·44)	3·22 (3·20–3·23)
History of E–Z vaccination	*n*	44	56	52	86	225	91	554
	% Pos. (CI)	82 (67–92)	82 (69–91)	89 (77–97)	74 (63–83)	86 (82–91)	98 (92–100)	86 (83–89)
	log GMT (CI)	3·02 (2·81–3·24)	2·74 (2·60–2·88)	2·80 (2·68–2·93)	2·81 (2·70–2·92)	2·75 (2·70–2·80)	2·92 (2·84–3·00)	2·81 (2·77–2·85)

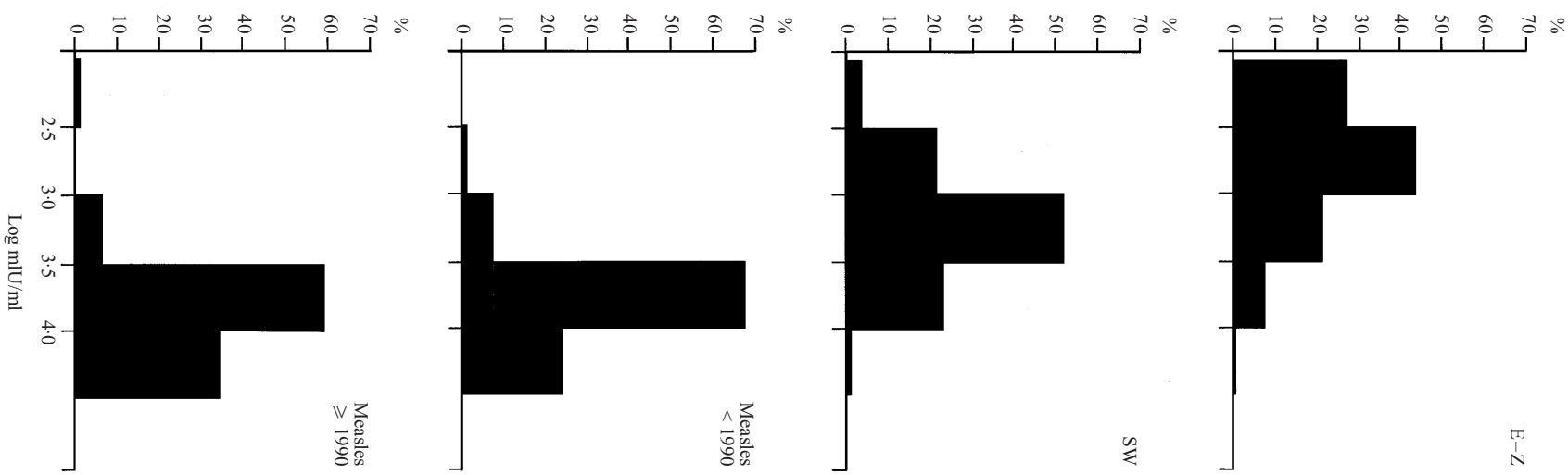

Fig. 2. Distribution of seropositive children by antibody titre and by history of measles or measles vaccination.

Table 3. *Number of subjects, percentage positive and log GMT values by history of measles or vaccination and by group*

	No history of measles/measles vaccination			History of measles						History of vaccination					
				< 1990			⩾ 1900			SW			E–Z		
Group	*n*	%	log GMT	*n*	%	log GMT	*n*	%	log GMT	*n*	%	log GMT	*n*	%	log GMT
A	204	23	3·42	240	92	3·80	35	80	3·79	1579	98	3·20	431	82	2·78
B	33	24	3·32	365	98	3·84	7	86	3·70	578	98	3·26	123	98	2·90
C	97	58	3·64	230	98	3·84	50	92	3·91	87	94	3·40	—	—	—
Comparison: among log GMT values*	$F = 3{\cdot}47$, $P = 0{\cdot}05$			$F = 1{\cdot}53$ (n.s.)			$F = 3{\cdot}70$, $P = 0{\cdot}05$			$F = 14{\cdot}5$, $P \ll 0{\cdot}001$			$F = 5{\cdot}96$, $P = 0{\cdot}01$		
% Positive†	$\chi^2 = 38{\cdot}1$, $P \ll 0{\cdot}001$			$\chi^2 = 19{\cdot}8$, $P \ll 0{\cdot}001$			$\chi^2 = 2{\cdot}62$, $P = 0{\cdot}27$			$\chi^2 = 4{\cdot}30$, $P = 0{\cdot}12$			$\chi^2 = 19{\cdot}3$, $P \ll 0{\cdot}001$		

* Analysis of variance was performed between groups A, B and C.

† Heterogeneity of percent of positive among groups A, B and C (χ^2).

Table 4. *Percentage positive* (*log GMT*) *by the interval between disease and blood sampling*

Special results	Interval between disease and blood sampling (years)			
	< 3	3–4	⩾ 5	Total
n	19	72	836	927
% Positive* (CI)	79 (61–97)	89 (82–96)	97 (95–98)	96 (94–97)
log GMT (CI)	3·95 (3·87–4·02)	3·83 (3·76–3·90)	3·83 (3·81–3·85)	3·83 (3·82–3·85)

* Test for trend was performed considering the percentage of positive serological result and interval (blood disease-sampling) $\chi^2_{\text{trend}} = 21{\cdot}7$, $P \ll 0{\cdot}001$.

B and C with a history of measles before 1990, who were positive was significantly higher than that in group A (98·4, 98·3 and 92·1%, $P < 0{\cdot}01$). No significant difference between groups was observed in percentage positive in children with a history of measles since 1990 (80·0, 85·7 and 92%, $P = 0{\cdot}27$). Percentage positivity in those having a history of SW vaccination was 97·7, 97·8 and 94·3% in groups A, B and C ($P = 0{\cdot}12$). Compared to 82·1 and 98·4% in group A and B ($P < 0{\cdot}01$) for E–Z vaccination.

Log GMT values were significantly higher in group C (3·64, 3·91 and 3·40) than in group A (3·42, 3·79 and 3·20) and group B (3·32, 3·70 and 3·26) for negative history of measles or measles vaccination ($P = 0{\cdot}05$), history of measles since 1990 ($P = 0{\cdot}05$) and history of SW vaccination ($P \ll 0{\cdot}01$) respectively. No difference in log GMT values was observed between groups for history of measles before 1990. Finally, log GMT values were significantly higher in group B than in group A (2·90 *vs*. 2·78, $P = 0{\cdot}01$) for E–Z vaccination.

Table 4 reports the number of subjects, percentage immunity and log GMT values according to the time interval between blood sampling and occurrence of measles. Whereas log GMT values do not differ significantly between the three intervals, there is a significant trend for the proportion of subjects immune: 78·9% for a time interval less than 3 years to 96·5% for a time interval greater than or equal to 5 years (χ^2 for trend, $P \ll 0{\cdot}01$).

Table 5 reports the number of subjects, percentage positive and log GMT values by vaccine strain and by the time interval between blood sampling and vaccination. Information on the date of vaccination was missing for 9 children vaccinated with E–Z and 23 with the SW strain. There is a clear trend in the proportion of immune subjects vaccinated with E–Z strain ($P = 0{\cdot}07$) but not among those vaccinated with SW strain ($P = 0{\cdot}63$). For each time interval, the percentage immunity for E–Z vaccinees is significantly lower than that observed in the SW vaccinees. Log GMT values range from 3·16 to 3·28 for vaccination with SW strain and 2·76 to 2·92 for E–Z strain. For each time interval, there is a significant difference in log GMT values between the SW and E–Z group.

Table 6 shows the results of the logistic regression analysis. Those vaccinated with the E–Z strain and those with an unknown source of vaccination have a higher risk of being susceptible (OR 7·60, 95% CI 4·66–12·4 and OR 2·92, 95% CI 1·30–6·51, respectively, adjusted for time interval and parents' level of education).

DISCUSSION

This study shows that during the 1989–91 Italian mass vaccination campaign, 96·5% of unvaccinated children with a history of measles (before 1990) were immune, compared to only 87·0% of those reporting measles since 1990. This confirms [6] the higher risk of a false diagnosis of measles after a large reduction in measles circulation (group A) and in the absence of indigenous measles (group B), compared to areas with only a small reduction in measles circulation (group C).

The high positive predictive value of history of measles as diagnosed by a physician without any standard case definition (before the mass vaccine campaign) is interesting. Our results stress the importance of an active surveillance system to identify the chain of transmission of measles cases after a mass vaccination campaign.

Among those vaccinated with SW vaccine 97·7% were immune, irrespective of time interval between vaccination and serological testing. In contrast, E–Z vaccine induced immunity in only 85·5%, and this declined as the time interval from vaccination increased. The log GMT value was 3·8 in those immune as a result of a history of measles and 3·2 and 2·8 among those vaccinated with SW or E–Z. Since

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Table 5. *Number of subjects, percentage positive and log GMT values by vaccine strain and by the interval between vaccination and blood sampling*

Serological results	Interval between vaccination and blood sampling (years)					
	< 3	3–4	5–6	7–8	⩾ 9	Total
SW						
n	291	799	539	406	186	2221
% Positive	96 (93–98)	99 (97–100)	98 (96–100)	98 (96–100)	96 (92–99)	98 (97–98)
log GMT	3·28 (3·23–3·33)	3·25 (3·22–3·27)	3·20 (3·18–3·24)	3·16 (3·13–3·20)	3·23 (3·18–3·28)	3·22 (3·20–3·23)
E–Z						
n	284	226	35	—	—	545
% Positive	88 (84–92)	83 (79–88)	80 (63–92)	—	—	86 (83–2·89)
log GMT	2·83 (2·78–2·89)	2·76 (2·70–2·81)	2·92 (2·74–3·09)	—	—	2·80 (2·77–2·84)
Comparison	$t = 11{\cdot}2$, $P \ll 0{\cdot}001$	$t = 16{\cdot}1$, $P \ll 0{\cdot}001$	$t = 3{\cdot}2$, $P < 0{\cdot}01$	—	—	$t = 18{\cdot}98$, $P \ll 0{\cdot}001$
Between log GMT values						
% Positive	$\chi^2 = 12{\cdot}0$, $P < 0{\cdot}001$	$\chi^2 = 95{\cdot}6$, $P \ll 0{\cdot}001$	$\chi^2 = 25{\cdot}7$, $P \ll 0{\cdot}001$	—	—	$\chi^2 = 145$, $P \ll 0{\cdot}001$

E–Z: $\chi^2_{\text{trend}} = 3{\cdot}36$, $P = 0{\cdot}07$.
SW: $\chi^2_{\text{trend}} = 0{\cdot}23$, $P = 0{\cdot}63$.

Table 6. *Result of logistic regression analysis. Adjusted odds ratio for risk of susceptibility in vaccinees*

	n	Adjusted OR*	95% CI†
Strain			
SW	2190	1	—
E–Z	541	7·60	4·66–12·4
Interval between blood sampling and vaccination			
< 1 year	165	1	—
2–3 years	920	1·17	0·61–2·25
4–5 years	836	1·09	0·50–2·39
6–7 years	442	1·23	0·49–3·05
⩾ 8 years	368	1·37	0·52–3·61
Applicant			
Public Health Service	2280	1	—
Private physician	375	1·28	0·78–2·10
Not known	76	2·92	1·30–6·51
Parents' level of education			
Low	1653	1	—
High	1078	1·19	0·81–1·72

* OR, odds ratio.
† CI confidence interval (95%).

92·1% of immune subjects vaccinated with the E–Z strain had log antibody titres less than 3·5, compared to only 8·8% of immune children with a history of measles, the assumption that almost all vaccinees were susceptible before vaccination is reasonable. Seroconversion rates after vaccination observed in this study are comparable to those found elsewhere when vaccine strain, quality of the vaccination practice (public or private), age at vaccination and effect of booster infection are considered [7–9].

The E–Z strain vaccine appears to have lower persistent immunogenicity than SW strain which could reduce the possibility of interrupting the circulation of measles.

Seroimmunity profiles of the three groups are consistent with residual circulation of measles after 1989. In group B, where mass vaccination campaigns were particularly successful (vaccine coverage in all age groups was 95–99%) and in which high coverage has been maintained in subsequent birth cohorts [4], only imported measles cases were identified by the active surveillance system. This implies that an immune profile of 95% or more, without spatial or age clusters of susceptibility, could guarantee the interruption of measles circulation [10].

In the region of Emilia Romagna, the mass vaccination campaign was equally successful among the local health units that participated in the sero-

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logical investigation (group A) as among those that did not. For this region it is possible to evaluate the effect of the programme on measles notifications by comparing the 10 years 1980–9 with the 5 years 1990–4. In this latter period the average notified measles incidence (per thousand, per year) has dropped from 10·5 to 1·8 (−82·9%), from 13·3 to 2·3 (−82·5%), from 3·9 to 2·3 (−40·3%) in the age groups 0–4, 5–9, 10–14 years, and from 1·4 to 0·5 (−67·8%) in the general population [1]. Given that the introduction of an active surveillance system should reduce the under-reporting of cases, the reduction in the number of cases observed after the vaccination programmes is probably an underestimate of the true reduction. How much the underreporting has changed in Italy as a whole and in the different geographical areas is a question for further research.

Because of the strong reduction (group A) or interruption (group B) of measles circulation in the period 1990–4, and that effect of booster infection on antibody levels can be considered negligible, it is reasonable to conclude that persistence of immunity induced by SW strain vaccines is long lasting. However, this is not the case for the E–Z strain, as found in other studies [11, 12]. The higher level of immunity observed in group B compared to group A may be explained by the fact that, E–Z vaccines were used in group B (only in Galatina district) since 1993, whereas in group A it has been used since it became available.

Even if the absence of detectable antibodies in E–Z vaccinees does not imply an absence of protection in all cases [13, 14], the suboptimal and declining immunity could be critical since a high level of herd immunity needs to be maintained to interrupt the circulation of measles in the community. It is an open question [15] if a second dose of measles vaccine is needed: our results suggest that it is more convenient to make sure that all susceptible subjects receive a single dose and, only subsequently, to consider the need of a second dose to achieve the elimination of measles [16].

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