

Measles seroepidemiology among adolescents and young adults: response to revaccination

M.J Saffar,¹ M. Alraza-Amiri,¹ A. Ajami,¹ F. Baba-Mahmoodi,¹ A.R. Khalilian,¹ C. Vahidshahi¹ and A. Shamsizadeh¹

وبائيات سيروولوجيا الحصبة بين المراهقين والبالغين: الاستجابة لإعادة التطعيم

محمد جعفر صفار، مهدي آل رضا أميري، أبو القاسم أعجمي، فرحناك بابا محمودي، علي رضا خليليان، كوروش وحيد شاهي، أحمد شمسي زاده

الخلاصة: قام الباحثون بتقييم معدل الانتشار المصلي لمستضدات الحصبة والاستجابة لإعادة التمنيع ضد الحصبة لدى 590 مراهقاً ويافعاً سبق تطعيمهم؛ فثبت أن 263 منهم سلبى المصل. وللتفرقة بين فشل اللقاح الأولي والثانوي، تم تقييم عيار الغلوبولين المناعي G والغلوبولين المناعي M بعد مضي 2-4 أسابيع من إعادة التطعيم لدى 144 فرداً، (فوجد أن 105 كانوا سلبيين المصل و39 إيجابيين المصل). وقد استجاب 75 من سلبيين المصل لإعادة التطعيم الإذكاري ($P < 0.001$) وظهرت لديهم المناعة، بينما أظهر 11 شخصاً استجابة للغلوبولين المناعي M (مما يشير غالباً إلى فشل اللقاح الأولي)؛ بينما ظلت الحماية المصلية متوافرة لنحو 38 من المشاركين إيجابيين المصل دون زيادة ملموسة في عيار المستضد ($P=0.577$). وقد كان معدل الإخفاق الأولي 4.7٪، والثانوي 27.1٪. أما بعد إعادة التطعيم فقد أصبح 87.3٪ محميين مصلياً.

ABSTRACT We evaluated the seroprevalence of measles antibody and response to measles reimmunization in 590 previously vaccinated adolescents and young adults; 263 were seronegative. To differentiate between primary and secondary vaccine failure, anti-measles IgM and IgG titres were assessed again 2-4 weeks after revaccination in 144 (105 seronegative, 39 seropositive) individuals: 75 seronegative participants responded to revaccination anamnestically ($P < 0.001$) and developed immunity, 11 also showed IgM response (probably primary vaccine failure); 38 seropositive participants remained seroprotected without significant increase in antibody titre ($P = 0.577$). Primary vaccine failure was 4.7%; secondary vaccine failure was 27.1%. After revaccination, 87.3% were seroprotected.

Séroépidémiologie de la rougeole chez des adolescents et de jeunes adultes : réponse à la revaccination

RÉSUMÉ Nous avons évalué la séroprévalence des anticorps antirougeoleux et la réponse à la revaccination contre la rougeole chez 590 adolescents et jeunes adultes ayant déjà été vaccinés ; 263 étaient séronégatifs. Pour faire la distinction entre l'échec vaccinal primaire et secondaire, le titre des anticorps IgM et IgG antirougeoleux a été réévalué 2-4 semaines après la revaccination chez 144 sujets (105 séronégatifs, 39 séropositifs) : 75 participants séronégatifs ont présenté une réponse anamnétique à la revaccination ($p < 0,001$) et ont développé une immunité, 11 ont également montré une réponse en IgM (probablement un échec vaccinal primaire) ; chez 38 participants séropositifs la séroprotection persistait sans augmentation significative du titre des anticorps ($p = 0,577$). L'échec vaccinal primaire était de 4,7 % ; l'échec vaccinal secondaire s'élevait à 27,1 %. Après la revaccination, 87,3 % étaient séroprotégés.

¹Department of Paediatrics, Paediatric Infectious Disease Ward, Bouali-Cina Hospital, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran (Correspondence to M.J. Saffar: saffar@softhome.net).

Received: 23/11/04; accepted: 28/02/05

Introduction

Despite the availability of a safe and effective vaccine, measles remains a public health problem worldwide. It has been estimated that 30 million people contract measles every year, and that nearly 1 million die. Many of the cases occur in adolescents and young adults [1-4]. Measles-related mortality also accounts for around 10% of all deaths in children < 5 years in developing countries [5].

There are only 2 reasons why older children remain susceptible to measles: failure to have been vaccinated and vaccine failure [6]. Vaccine failure remains a major obstacle that must be overcome before measles can be controlled [7]. Primary vaccine failure (PVF) is failure of immediate seroconversion, with a documented lack of detectable specific antibody. Administration of a second dose of vaccine results in a high proportion undergoing a primary antibody response, with an initial IgM response followed by IgG seroconversion. Secondary vaccine failure (SVF) results when there is initial documented seroconversion in response to vaccination followed by loss of protection, usually linked to waning serum antibody levels [8]. On exposure to measles virus, an individual may contract the virus and only show anamnestic type of antibody response, or may become ill. Following a second dose of vaccination, a large boost in IgG antibody levels generally occurs, with little or no IgM response [8].

Around 95%–98% of individuals who receive a single dose of measles vaccine after 12 months of age develop measles antibodies [9]. Some studies have shown that children vaccinated twice have better protection than single dose recipients [8,9]. The measles vaccine is, however, less

immunogenic in the presence of maternal antibodies before 12 months of age [8], and some studies showed that additional doses of vaccine could not boost the antibodies to a satisfactory level, and that any boosting that did take place was only short-lived [7,10,11].

Since 1981, through the Expanded Programme on Immunization, the World Health Organization has recommended a single dose of measles vaccine at 9 months of age in countries where measles is a problem in the first year of life [12]. Despite this programme, measles continues to be a major child health problem in developing countries [6,13].

The Iranian immunization policy follows the World Health Organization's recommendation for developing countries, and includes a monocomponent vaccine against measles at 9 months of age [12]. In addition, the Iranian Ministry of Health recommends that a second dose of the measles vaccine be given at the age of 15 months. After implementing the 2-dose vaccination schedule with high levels of coverage (> 95%), between 1988 and 1998 the incidence of measles decreased markedly in Iran. During recent years, however, the incidence of the disease has been increasing, with some incidences in previously vaccinated individuals among all age groups, mainly adolescents and young adults [14,15].

This study was designed to determine the probable causes of this resurgence in measles cases, especially in adolescents and young adults who had been vaccinated against measles according to the Iranian vaccination schedule. We also evaluated the IgM and IgG antibody responses to reimmunization with measles-containing vaccine to differentiate PVF from SVF.

Methods

Participants

This study was carried out from October 2003 to February 2004. Healthy volunteers [with no history of medical problems (e.g. acute respiratory infection, febrile illnesses, skin rash), physician-diagnosed measles or chronic illness] between 15 and 25 years of age were recruited from the student population at Mazandaran University of Medical Sciences and at several secondary schools from different areas of Sari, the capital of Mazandaran province. Medical students were recruited through flyers circulated in the university and volunteers selected based on medical vaccination records (recipients of 1 dose of measles vaccine). High-school students were selected based on medical vaccination records (recipients of 2-dose measles vaccine) and student population density. If a student refused to participate, the next student was substituted. We did not have a substantial refusal rate.

Written informed consent was obtained from all participants. For volunteers under the age of 18 years, informed consent was also obtained from a parent. The protocol was reviewed and approved by the Medical Ethics Committee of the university.

Vaccine histories of the participants were obtained from the primary health centre vaccine records. Up to 1982, measles vaccination policy in the Islamic Republic of Iran was to administer 1 dose of the vaccine after the age of 12 months (Measles vaccine, Bio-Merieux, France). The 1981 recommendations of the Expanded Programme on Immunization for measles vaccination for developing countries have been implemented in the Islamic Republic of Iran since 1983 [6], with some modification, i.e. 2 doses of measles vaccine administered at 9 and 15 months of age (Measles vaccine, Razi Institute, Tehran).

Blood sampling

For initial screening, 5 mL of venous blood was drawn from each participant under the supervision of one of the researchers. Samples were taken during October 2003–December 2003 and for the second phase during January 2004–February 2004. Sera were stored at -20°C until assayed. As part of the measles–rubella mass vaccination programme in the Islamic Republic of Iran (6–31 December 2003), all individuals 5–25 years of age were vaccinated with measles–rubella virus-containing vaccine (Serum Institute of India Ltd, Pune), i.e. all those in the study sample were revaccinated after the first blood sampling. Sera were obtained 2–4 weeks after revaccination to determine the IgM and IgG antibody responses to revaccination.

Serologic assay

Measles IgG and IgM antibodies were detected by enzyme-linked immunosorbent assay (Measles IgM-ELISA and measles IgG-ELISA, IBL, Hamburg). The tests were performed in the university laboratory according to the manufacturer's instructions. Quantitative antibody titres < 10 IU/mL were reported as negative and ≥ 10 IU/mL as positive. All sera (samples obtained before and after revaccination) were tested for IgG measles-specific antibodies; IgM was measured only in blood samples taken after revaccination to differentiate primary and secondary response types.

Statistical analysis

Data were analysed as ordinal and continuous variables. Antibody levels were log-transformed for calculation of geometric mean antibody concentrations. The student *t*-test was used to compare the mean values in the pre- and post-vaccination groups. All statistical analysis was performed using SPSS, version 10.

Results

A total of 590 adolescents and young adults (39.7% female), mean age 21.1 years [standard deviation (SD) 5.0; range 15–25 years], were enrolled into the measles seroprevalence study trial and underwent serological screening for measles-specific IgG antibody. All of these individuals had previously received measles vaccine, 2 doses (at 9 months and 15 months) in the 209 participants 15–19 years old and 1 dose (after 12 months) in the 381 participants aged 20 years and older, as part of the routine measles vaccination schedule in the Islamic Republic of Iran.

We found that 263 (44.6%) participants were serologically negative for measles antibody, geometric mean concentration 4.09 (SD 2.6) IU/mL mean age 20.0 (SD 2.9) years, and 327 (55.4%) were seropositive, geometric mean concentration 56.5 (SD 45.3), mean age 22.2 (SD 7.0). The results of the serological assays are summarized in Table 1.

All 590 individuals were revaccinated (as part of the catch-up programme, 6–31 December 2003), and 105 participants identified as seronegative and 39 identified as seropositive agreed to provide blood samples for follow-up studies. Seventy-five

of the revaccinated seronegative individuals (71.4%) responded to revaccination and showed significant increase in the levels of IgG measles antibody ($P < 0.001$) (Table 2); 11 (10.5%) also showed IgM response (probably primary vaccine failure). Of the 39 revaccinated seroprotected individuals, 38 remained seropositive with no statistically significant increase in IgG measles antibody. No IgM response was detected in this group.

To understand the effect of vaccine dose at initial immunization on seropositivity, response to reimmunization and amount of time elapsed between initial immunization and revaccination, we compared the seropositivity rates and responses to revaccination in 2 age groups: 15–19 years (previously received 2 doses of measles vaccine) and 20 years and older (previously received 1 dose of measles vaccine). As shown in Table 1, 103 (49.2%) of the 209 people in the younger group and 160 (42.0%) of the 381 in the older group were seronegative, $P = 0.16$.

Also, 65.8% of the revaccinated individuals enrolled in the younger (2 dose) group responded to revaccination compared to 91.3% in the older (single dose) group (Table 3). Based on these results, extrapola-

Table 1 Seroprevalence status of adolescents and young adults before measles revaccination, Sari, Islamic Republic of Iran

Measles seroprevalence	Total (n = 590)		Participants Age 15–19 years (n = 209)		Participants Age 20–25 years (n = 381)	
	No.	%	No.	%	No.	%
Antibody positive ^a	327	55.4	106	50.8	221	58.0
Antibody negative ^b	263	44.6	103	49.2	160	42.0
GMC (SD) (IU/mL)	30.3 (24.0)		59.7 (48.4)		53.3 (42.2)	

GMC = geometric mean antibody concentration.

SD = standard deviation.

^aGMC 4.09 (SD 2.6).

^bGMC 56.5 (SD 45.3).

Table 2 Comparison of response to revaccination between seronegative and seroprotected individuals, Sari, Islamic Republic of Iran

Variable	IgG response		IgM response		GMC				P-value
	No.	%	No.	%	Pre- vaccination Mean	SD	Post- vaccination Mean	SD	
Seronegative (n = 105)	75	71.4	11	10.5	4.2	2.6	37.5	44.2	< 0.001
Seropositive (n = 39)	38	97.4	0	–	68.3	64.4	63.0	56.4	0.577

GMC = geometric mean antibody concentration.

SD = standard deviation.

tions can be made regarding PVF, SVF and efficacy of initial vaccination and revaccination programmes. Thus, PVF was estimated at 4.7% $[(263 \times 100 \times 11)/(590 \times 105)]$ and SVF at 27.1% $[(263 \times 64 \times 100)/(590 \times 105)]$ and total vaccination and revaccination efficacy was estimated at 87.3% $[327 + (263 \times 75)/(590 \times 105)]$, so community immunity on 95% vaccination coverage would be 82.9% $[(87.3 \times 95)/100]$, where 590 = total no. participants in primary screening, 263 = no. seronegative in primary screening, 105 = no. seronegative after revaccination, 75 = no. responding to revaccination (IgM, IgG), 64 = no. seronegative responding with IgG response only (probably SVF), 11 = no. seronegative responding with IgM (probably PVF) and 327 = no. immune in primary screening.

Table 3 Comparison of response to revaccination in seronegative individuals according to number of doses of measles vaccine originally given

Doses	Total (n = 105)	Responded	
		No.	%
2	82	54	65.9
1	23	21	91.3

Discussion

In this study we measured anti-measles IgG antibody titres 15 to 25 years after 1 or 2 doses of measles vaccination to determine the proportion of seropositivity. Of the studied population 44.6% were seronegative, and there was no difference between those who had had 1 dose of vaccine and those who had had 2 doses ($P = 0.16$).

Reinfection and disease seem to occur in individuals who have previously had a measles immunization and when the titre has fallen below a critical level [16,17]. Vaccine failure may occur either because the immune response never developed or because it waned over time [18,19]. Reported rates of primary vaccine failure vary widely (0–74%) [8]. Some studies documented lower rates of seroconversion when the first immunization was given before 12 months of age [7,10,11]. Linnemann et al. found that 40% of children who had received 2 doses of measles vaccine (first dose before 12 months of age) were seronegative, and 33% of the seronegative ones did not respond to a third dose of vaccine [10]. Studies on seroconversion rates in children after the first and second doses of measles vaccination at 9 and 15 months of age showed seroconversion rates of 77.6% and 69.9% after the first dose and 81.9%

and 90.3% after the second dose of measles vaccine [20,21].

The phenomenon of SVF due to waning immunity may become apparent only after the passage of years. There is some indication that antibody titres fall to low or undetectable levels in populations with little re-exposure. This problem may be greater in areas where immunization was introduced early and the initial antibody response was lower [19,12–26]. The findings of a study on long-term persistence of antibody titres induced by vaccination and natural infection suggest that vaccine-induced measles antibodies decline with time, and fall below protective levels [19]. Results of a study from China indicated that 14 years after primary immunization, around 10% of those vaccinated had lost their protective levels, with antibody titres beginning to convert to negative between the third and sixth year after immunization [26].

In our study, after revaccination, 71.4% of 105 people who were seronegative showed IgG antibody response to revaccination. However, no significant increase in antibody level was observed in the 39 seropositive individuals we examined. These results are comparable with the findings of other studies. Cohen et al. demonstrated that 58% of seronegative individuals 10–30 years of age developed measles-specific IgG titres that remained positive at least 1 year after revaccination, and the remainder either developed only a transient response (30%) or never developed a positive titre (12%) [27]. Poland et al. showed that 19.2% of people vaccinated were seronegative 4–11 years after the primary series of vaccination and 18.5% of 130 seronegative individuals remained seronegative after revaccination [28]. In an investigation on a measles outbreak in a fully vaccinated school population, 18% of 239 sera (26% of those > 17 years) collected from students just before revaccination were negative for

measles antibodies, and 7.9% of students were unprotected against illness with rash and 44.8% against measles without rash; 9 to 11 months after revaccination these rates were 3% and 45%, respectively [29]. Two other studies showed that people with protective levels of antibodies did not respond to revaccination anamnesticly, but seronegative individuals did, although perhaps temporarily [24,30].

To determine whether the seronegativity had been induced by PVF or SVF, the IgM antibody responses were assayed. Eleven of 105 (10.47%) seronegative individuals showed IgM antibody response after revaccination, the results suggested that they probably were a result of PVF. The lack of an IgM response in other responders suggests the previous response to vaccination had been lost over time [7].

Recent successes in interrupting measles transmission in the World Health Organization Region of the Americas, most other countries in Europe and selected countries in other regions provide evidence for the feasibility of global eradication [31–35]. The World Health Organization has developed a global plan for accelerated measles control which calls for implementation of a strategy based on that used to successfully control measles in the Pan American Health Organization (PAHO): a catch-up campaign providing measles vaccine to all children regardless of prior history of immunization or disease, followed by high levels of routine coverage with measles immunization (keep-up) and periodic follow-up campaigns targeting all children 1–4 years of age [35].

To interrupt virus transmission in a community, > 95% of a population must be protected. It seems impossible to reach a sufficiently high level of protection by routine vaccination. In this study among adolescents and young adults in Mazandaran 15–25 years after scheduled measles vacci-

nation, PVF and SVF were 4.7% and 27.1% respectively. After revaccination, 87.3% of those vaccinated developed immunity. Considering the vaccine coverage of 95% and efficacy of 87%, only 83% of individuals would be immune, a rate which may not prevent measles outbreaks.

Conclusion

Based on the results of this and previous studies on measles epidemiology in Mazandaran

and the rest of the country [14,15], and also taking into account experiences on measles control in other parts of the world [31–34], we advise the implementation of World Health Organization-recommended strategies to reduce and interrupt indigenous measles virus transmission in the Islamic Republic of Iran. Mass vaccination with a keep-up phase and follow-up cyclic campaigns would reduce the number of susceptible individuals and to prevent new outbreaks.

References

1. Hersh BS et al. Review of regional measles surveillance data in the Americas, 1996–99. *Lancet*, 2000, 355(9219):1043–8.
2. Study of measles epidemiology in Iran during 1991 to 1998. Annual report of the Minister of Health and Medical Education. Tehran, Ministry of Health and Medical Education, 1998.
3. Miller M, Williams WW, Redd SC. Measles among adults, United States, 1985–1995. *American journal of preventive medicine*, 1999, 17(2):114–9.
4. Centers for Disease Control and Prevention. Progress toward measles elimination—Region of the Americas, 2002–2003. *Morbidity and mortality weekly report*, 2004, 53(14):304–6.
5. Chalmers I. Why we need to know whether prophylactic antibiotics can reduce measles related morbidity. *Pediatrics*, 2002, 109(2):12–5.
6. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bulletin of the World Health Organization*, 1993, 71(3–4):421–8.
7. Wilkins J, Wehrle RF. Additional evidence against measles vaccine administration to infants less than 12 months of age: altered immune response following active/passive immunization. *Journal of pediatrics*, 1979, 94(6):865–9.
8. Redd SC, Markowitz LE, Katz SL. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*, 3rd ed. Philadelphia, WB Saunders, 1999:222–66.
9. Measles. In: Pickering LK, ed. *Red book: 2003 Report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, American Academy of Pediatrics, 2003:419–29.
10. Linnemann CC Jr et al. Measles immunity after revaccination: results in children vaccinated before 10 months of age. *Pediatrics*, 1982, 69(3):332–5.
11. Stetler HC et al. Impact of revaccinating children who initially received measles vaccine before 10 months of age. *Pediatrics*, 1986, 77(4):471–6.
12. Expanded Programme on Immunization, Global Advisory Group. *Weekly epidemiological record*, 1981, 56(2):9–16.
13. Mitchell LA et al. Serologic responses to measles, mumps, and rubella (MMR) vaccine in healthy infants: failure to respond to measles and mumps components may influence decisions on timing of the sec-

- ond dose of MMR. Canadian journal of public health, 1998, 89(5):325-8.
14. Azmoodah M. Epidemiology of measles in Iran, year 1998. Paper presented at the 8th Iranian congress of infectious diseases and tropical medicine, Tehran, 16-20 January 2000 (in Farsi).
 15. Saffar MJ et al. Epidemiology of measles in Mazandaran province, year 2000-2002. Namah Daneshgah (journal of Mazandaran University of Medical Sciences), 2006, 16(52):48-56 (in Farsi).
 16. Gustafson TL et al. Measles outbreak in a fully immunized secondary-school population. New England journal of medicine, 1987, 316(13):771-4.
 17. Chen RT et al. Measles antibody: reevaluation of protective titers. Journal of infectious diseases, 1990, 162(5):1036-42.
 18. Mathias RC et al. The role of secondary vaccine failure in measles outbreaks. American journal of public health, 1989, 79:475-8.
 19. Christensen B, Bottiger M. Measles antibody: comparison of long-term vaccination titres, early vaccination titres and naturally acquired immunity to and booster effects on the measles virus. Vaccine, 1994, 12(2):129-33.
 20. Isik N et al. Seroconversion after measles vaccination at nine and fifteen months of age. Pediatric infectious diseases journal, 2003, 22(8):619-25.
 21. Ceyhan M et al. Immunogenicity and efficacy of one dose measles-mumps-rubella (MMR) vaccine at twelve months of age as compared to monovalent measles vaccination at nine months followed by MMR revaccination at fifteen months of age. Vaccine, 2001, 19(31):4473-8.
 22. Edmonson MB et al. Mild measles and secondary vaccine failure during a sustained outbreak in a highly vaccinated population. Journal of the American Medical Association, 1990, 263(18):2467-71.
 23. Markowitz LE et al. Duration of live measles vaccine-induced immunity. Pediatric infectious diseases journal, 1990, 9(2):101-10.
 24. Davidkin I, Valle M. Vaccine-induced measles virus antibodies after two doses of combined measles, mumps and rubella vaccine: a 12-year follow-up in two cohorts. Vaccine, 1998, 16(20):2052-7.
 25. Whittle HC et al. Effect of subclinical infection on maintaining immunity against measles in vaccinated children in West Africa. Lancet, 1999, 353(9147):98-102.
 26. Cai B et al. Duration of immunity following immunization with live measles vaccine: 15 years of observation in Zhejiang province, China. Bulletin of the World Health Organization, 1999, 69(4):415-23.
 27. Cohn ML et al. Measles vaccine failure: lack of sustained measles-specific immunoglobulin G responses in revaccinated adolescents and young adults. Pediatric infectious diseases journal, 1994, 13(1):34-8.
 28. Poland GA et al. Measles reimmunization in children seronegative after initial immunization. Journal of the American Medical Association, 1997, 277(14):1156-8.
 29. Matson DO et al. Investigation of a measles outbreak in a fully vaccinated school population including serum studies before and after revaccination. Pediatric infectious diseases journal, 1993, 12(4):292-9.
 30. Markowitz LE et al. Persistence of measles antibody after revaccination. Journal of infectious diseases, 1992, 166(1):205-8.
 31. De Quadros CA et al. Measles eradication: experience in the Americas. Bulletin of the World Health Organization, 1998, 76(suppl. 2):47-52.
 32. Biellik R et al. First 5 years of measles elimination in Southern Africa: 1996-2000. Lancet, 2002, 359(9317):1564-8.

33. Uzicanin A et al. Impact of the 1996–1997 supplementary measles vaccination campaigns in South Africa. *International journal of epidemiology*, 2002, 31(5):968–76.
34. De Quadros CA et al. Measles eradication in the Americas: progress to date. *Journal of infectious diseases*, 2004, 189(suppl. 1):S227–35.
35. De Quadros CA. Can measles be eradicated globally? *Bulletin of the World Health Organization*, 2004, 82(2):134–8.

Measles elimination

In 1997, the Regional Office established a goal to eliminate measles by 2010. The regional strategy for measles elimination includes: high routine measles vaccination coverage (> 90%) among children aged 1 year; one-time, nationwide mass immunization campaign or catch-up campaign targeting all children; second opportunity for measles immunization either through periodic follow-up campaigns every 3–5 years targeting all children born since the last campaign or achieving > 95% routine coverage with a second dose of measles vaccine; and optimal case management of children with acute disease.

Raising coverage with ≥ 1 dose of measles-containing vaccine is a key element of the elimination strategy. In 2005, coverage was 82%, leaving an estimated 2.8 million children who were not vaccinated. More than 90% of these children reside in Afghanistan, Iraq, Pakistan, Somalia, Sudan and Yemen. In 2005, Afghanistan, Iraq, Sudan and Yemen made considerable progress in increasing coverage, and it is anticipated that this will continue.

Estimated regional deaths due to measles, 1999–2004

Year	Estimated deaths
1999	102 000
2000	105 000
2001	89 000
2002	59 000
2003	58 000
2004	46 000

Based on campaign results, surveillance data and routine EPI coverage, reduction in measles mortality has been > 50% since 1999.

Source: DCD Newsletter Issue no. 8, June 2006 (<http://www.emro.who.int/pdf/dcdnewsletter8.pdf>).