

Two-Dose Measles Immunization as a Strategy to Eliminate Measles in the Middle East and Israel

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Measles is still a significant cause of morbidity and mortality in children in the Middle East. This region has many hard-to-reach populations, causing difficulties in the provision of adequate immunization coverage.

There has been concern that measles vaccine may produce transient immunosuppression in malnourished children and thereby increase their risk for the development of infectious diseases in the immediate post-immunization period. Since the Middle East has a relatively high rate of children suffering from chronic malnutrition, it is important to assess the immune response of these children to measles immunization in order to provide assurance that the measles vaccine, while effective in preventing measles, does not increase the risk for other infectious diseases.

Israel is officially part of the European Region of the World Health Organization but belongs geographically to the Middle East. Other countries in the Middle East are included in the Eastern Mediterranean Region of the WHO. This paper reviews the progress made in Israel and the Eastern Mediterranean Region of the WHO towards achieving the WHO goal of the elimination of measles by the year 2010. In addition, this review summarizes data on humoral and cellular immune responses to measles vaccine that is relevant for programs targeted at the prevention of measles in populations suffering from malnutrition.

Effects of measles vaccine on humoral and cellular immunity

Measles virus infection is associated with immune suppression, including impaired humoral and cellular immunity, and can be a devastating illness in a malnourished population as it increases susceptibility to secondary infections [1,2]. However, there is concern that malnutrition may also affect the immune response to measles vaccine [1,3]. It is therefore important to review studies investigating the immune response to measles immunization.

The Bedouin Arab population in Israel is a population of low socioeconomic status in which 11–17% of infants aged 1–2 years and 6–10% of infants less than one year of age in 1992 were found to be stunted [4]. In 1995, in order to determine if Bedouin Arab infants of low socioeconomic status develop

an adequate immune response to routine measles-mumps-rubella immunization, the responses of 12 month old Bedouin infants (of low socioeconomic status) were compared to those of Jewish infants (of middle-class socioeconomic status) 30 days after primary MMR immunization. Contrary to expectations, the Bedouin infants were found to have a significantly higher rate of seroconversion to measles (99%) than did Jewish infants (79%) as well as significantly higher measles neutralizing antibody titers [5]. Immunoglobulin G levels were higher in Bedouin than Jewish children both before and after immunization, while IgM and IgE levels were not significantly different between Bedouin and Jewish children [5]. Cellular immune responses to measles vaccine were also studied in this population and no adverse effects of vaccination on immune function were detected. This study of humoral and cellular immune responses to measles immunization indicates that in a population of lower socioeconomic class Bedouin Arab children, measles immunization produces adequate immunological responses with no adverse effect on immune function [5].

Since an estimated 2 to 10% of infants who receive primary immunization fail to produce protective antibodies [5], a second dose of measles vaccine is critical. There has been concern that re-immunization may have adverse immunological consequences. To determine the effects of re-immunization on the immune response, schoolchildren in Beer Sheva with documented MMR vaccination during infancy were studied before and 1 month after receiving a second dose of MMR [6]. The geometric mean titer of measles virus neutralizing antibody titer increased from 171 to 724 IU/ml. There was little evidence of functional impairment of lymphocytes, with overall improvements in proliferation to *in vitro* mitogen and recall antigen stimulation and retention of natural killer cell lytic activity. The re-immunization of 6 year old children with MMR was effective and there were no significant adverse effects on immune function [6]. Similar results were found in a study of the effects of re-immunization on the immunological system in young adults in the United States [7]. It was found

MMR = measles-mumps-rubella

Ig = immunoglobulin

that measles re-immunization activates multiple cellular mechanisms that can override the immunosuppressant effects of the measles virus [7].

In a study of 755 Israeli children who received MMR immunization between May 1993 and April 1994, Shohat et al. [8] found no gender differences in anti-measles antibody titers 1 month post-immunization and no correlation between antibody titers and the appearance of symptoms and illnesses in the 1 month follow-up.

Measles immunization produces adequate immunological responses with no significant effect on immune function, even among children of low socioeconomic status who suffer from poor nutrition

The humoral antibody response to measles immunization has been reported from other countries of the region (Egypt, Jordan, Iran, Saudi Arabia, Yemen) [9-13]. In none of these studies was an association mentioned between antibody response and nutritional status of the study population. No studies on cellular immunologic response to measles immunization could be found in the literature among populations in the Middle East other than those mentioned above, which were carried out in an Israeli population.

These data indicate that neither primary nor secondary measles immunization produces adverse affects on humoral or cellular immunity, even among children of low socioeconomic status. Measles immunization can be safely administered to low socioeconomic status children with no expected decrease in the ability of the vaccine recipient to mount an immunological response to the vaccine or to other infectious diseases to which they might be exposed.

Immunization policy and its effect on the incidence of measles in the Eastern Mediterranean Region of the WHO

Measles infection is still a major cause of morbidity and one of the 10 major causes of death due to infectious diseases in children in the world, causing an estimated 454,000 deaths in 2004 [14,15]. Although measles is considered a vaccine-preventable disease, it represents 50–60% of the deaths attributed to vaccine-preventable diseases [1,15].

The Middle East is a region with a high rate of poverty and malnutrition. An estimated 23% of the children in the Middle East and North African Region of the WHO suffer from malnutrition as measured by height-for-age less than 2 SD below the median of an international reference population [16]. It is therefore instructive to examine the success of a targeted program to eliminate measles in the region.

Table 1. Reported vaccine coverage of first dose of measles vaccine in Israel and countries of the Eastern Mediterranean Region of the WHO in 1990, 2000 and 2005 and current measles immunization schedule

Country	1990 %	2000 %	2005 %	Immunization schedule 2005
Israel	91	94	96	12 mos; 6 yrs
Afghanistan	20	35	64	9 mos; 18 mos
Bahrain	87	98	100	1, 5, 12 yrs
Djibouti	85	50	65	9 mos; 24 mos
Egypt	87	98	98	9 mos; 18 mos
Iran	85	99	94	12 mos; 4-6 yrs
Iraq	83	93	85	9 mos; 15 mos; 6 yrs
Jordan	87	94	95	9 mos; 18 mos
Kuwait	66	99	97	1, 3.5 yrs
Lebanon	39	90	54	13 mos; 4-5 yrs
Libya	89	NA	97	9, 18 mos
Morocco	79	93	97	9 mos; 6 yrs
Oman	98	99	98	12 mos; 18 mos
Pakistan	76	75	78	9 mos
Qatar	79	91	100	12 mos; 4-6 yrs
Saudi Arabia	88	94	97	1, 4-6 yrs
Somalia	30	35	35	9 mos
Sudan	57	60	73	9 mos
Syria	87	94	98	10 mos; 15 mos
Tunisia	85	92	96	15 mos; 6 yrs; 12 yrs
United Arab Emirates	80	94	92	9 mos; 15 mos; 6 yrs
Yemen	74	71	76	9, 18 mos

NA = data not available.

Ref: WHO vaccine-preventable diseases: monitoring system. 2006 global summary. Immunization, Vaccines and Biologicals. WHO. Printed: November 2006. www.who.int/vaccines-documents/

Countries belonging to the Eastern Mediterranean Region of the WHO designed a program in 1997 whose goal was to eliminate measles by the year 2010 [17]. The proposed program included several components: measles vaccination coverage of at least 95% at age 1 year; one-time mass vaccination campaigns (catch-up campaign); periodic national follow-up campaigns; strengthening measles surveillance; and laboratory confirmation of cases.

Table 1 shows the reported vaccine coverage achieved by the year 2000 for the countries in the region, and the reported annual incidence rates for measles are shown in Table 2. The incidence rate of measles was reduced but the goal of eliminating measles was not achieved. This was not surprising in light of the fact that 2–10% of infants immunized at age 12 months are not protected by one dose of measles immunization [5]. Throughout the world, outbreaks of measles have occurred in populations with high immunization coverage for one dose of measles immunization, indicating the failure of the one-dose policy in the control of measles [18]. Rosenthal and Clements [19] reviewed the potential for a two-dose policy to improve measles control in the *Bulletin of the World Health Organization* in 1993, while in the

Table 2. Reported measles incidence in Israel and countries of the Eastern Mediterranean Region of the WHO in 1990, 2000 and 2005

Country	1990 Incidence/ 100,000	2000 Incidence/ 100,000	2005 Incidence/ 100,000
Israel	5.1	0.6	0.02
Afghanistan	11.0	27.5	4.3
Bahrain	11.9	0.9	0.6
Djibouti	18.6	25.6	37.6
Egypt	1.6	3.9	0.1
Iran	9.4	17.9	0.01
Iraq	16.5	2.9	3.2
Jordan	8.9	0.6	0.5
Kuwait	3.31	0.27	0.37
Lebanon	NA	0.15	17.28
Libya	21.48	NA	498
Morocco	6.39	25.2	20.6*
Oman	68.5	0.6	0.97
Pakistan	19.5	1.5	1.89
Qatar	67.2	7.6	9.1
Saudi Arabia	33.2	0.7	1.5
Somalia	NA	56.54	150.7*
Sudan	53.99	8.74	3.79
Syria	4.17	0.87	1.96
Tunisia	6.66	0.49	0.14
United Arab Emirates	63.5	2.1	0.65
Yemen	NA	2.62	29.96
All countries	15.67	7.98	2.8

NA = data not available.

* 2004 rate

Ref: WHO vaccine-preventable diseases: monitoring system. 2006 global summary. Immunization, Vaccines and Biologicals. WHO. Printed: November 2006. www.who.int/vaccines-documents/

same issue Tulchinsky et al. [18] presented their opinion that a two-dose measles immunization policy is an essential component of measles control, along with data showing highly favorable cost-benefit analysis for a two-dose strategy.

First dose at age less than 12 months often does not produce a significant antibody response [20]. Therefore, infants who receive their first dose of measles immunization at 6–11 months of age need to have a repeat dose at 12 months [19]. For countries that routinely give the first dose of measles immunization at less than 12 months of age, a repeat dose is recommended at 12 months with a booster at school entry [19].

In 2001, the WHO and UNICEF developed a joint strategy for reduction in measles mortality in high priority countries, with a recommendation for a second dose of measles immunization, as well as targets for high rates of coverage for routine measles immunization ($\geq 90\%$). WHO data on immunization coverage for the first dose of measles immunization for every country in the Eastern Mediterranean Region of the WHO are given in Table 1, along with a summary of the current immunization policy of

each country. Immunization coverage is presented for the year 1990 (before the introduction of targeted programs to eliminate measles), for the year 2000 (before the recommendation that all countries in the region adopt a two-dose strategy), and for the last year for which data were published by the WHO (2005) [21]. There has been a rise in reported immunization coverage for first-dose measles immunization in countries of the Eastern Mediterranean Region, with 13 of the 21 countries reporting immunization coverage above 90% in 2005 while only 1 country reported immunization coverage above 90% in 1990. Only 10 of 21 countries in the Eastern Mediterranean Region currently have a policy of measles immunization, which includes both a dose at age 12–15 months as well as an additional dose at age 3–6 years.

It is impressive that many countries of the Eastern Mediterranean Region of the WHO have managed to reach the target goal for first dose of measles immunization. This region has many difficult-to-reach populations in rural villages and in crowded urban centers, as well as nomads who follow their herds of sheep, goats and camels from one grazing ground to another.

The results of programs in Iran and Saudi Arabia present interesting case studies. Iran has had high coverage for first dose of measles ($> 94\%$) for the past decade and a two-dose policy since 1984. However, there were still many cases of measles. They therefore undertook a mass immunization campaign in December 2003 targeting the immunization of 33,579,082 people between the ages of 5 and 25 years. They achieved immunization coverage of 92% for the second dose by 2005 [22]. A post-campaign survey found that more than 97% had immunity to measles. The number of reported cases of measles dropped dramatically and now stands at less than 1 per million, with sporadic cases occurring primarily among immigrant and nomadic populations [23].

Saudi Arabia has made major efforts to control measles in the past two decades. Mandatory measles immunization was introduced in 1982 for infants less than 12 months old. In 1991 the policy was changed to include a first dose at 6 months of age with a second dose at 12 months. Immunization coverage for the dose at 12 months was above 90%. There was a marked reduction in the severity of epidemics, but 50% of cases of measles in children aged 1 to 4 years occurred in previously immunized children, indicating the need to add a dose in children older than 12 months [20,24]. The current immunization policy of Saudi Arabia is a three-dose strategy (9 months, 12 months, 4–6 years). The reported incidence rate of measles dropped from 33.2/100,000 in 1990 to 1.5/100,000 in 2005 [21].

Reported incidence rates of measles before and after the introduction of targeted WHO programs aimed at the elimination of measles appear in Table 2 for all countries of the Eastern Mediterranean Region of the WHO. Reported incidence rates for all countries of the region decreased from 15.67/100,000 in 1990 to 7.98/100,000 in 2000 and 2.8/100,000 in 2005.

The rise in reported immunization coverage for the first dose of measles immunization, as well as the introduction of a two-dose immunization schedule, has been associated temporally with a decrease in reported incidence of measles in the Eastern

Mediterranean Region of the WHO. We have no data on the reliability of the reported rates of immunization coverage or on reported incidence rates of measles in the region.

There has been a marked reduction in the incidence of measles in the Middle East since the introduction of targeted programs by the WHO and UNICEF to reduce measles morbidity and mortality

Immunization policy and its effect on incidence of measles in Israel

Israel has a systematic system for monitoring immunization coverage and for diagnosis and reporting of measles cases. In Israel, coverage for first dose of measles immunization was 91% in 1990 (before the introduction of a second-dose policy) and 96% in 2005 [21]. Data on 18 year old army recruits in Israel from 1990 showed that 29% had low levels of immunity to measles at a time when a one-dose immunization policy was in effect [25]. The authors concluded that the potential still existed in Israel for periodic outbreaks of measles. A two-dose policy was adopted by Israel in 1990, with the first dose at age 12 months and a second dose at school entry. Immunization coverage in Israel for the second dose of measles immunization (administered in first grade) was 97% in 2005 [22]. After the introduction of a two-dose policy in 1990, there has been a marked decrease in the annual incidence of measles in Israel, along with a decrease in the frequency and severity of outbreaks of measles.

Before the introduction of an immunization program for measles in 1967, Israel was a country with incidence rates ranging from 2038.77 to 58.04 per 100,000. After the introduction of the vaccine, incidence rate declined to 4 per 100,000 in 1971. However, despite routine immunization against measles, periodic outbreaks did occur [26].

In 1990 a booster vaccine dose for first-grade pupils was introduced into the routine immunization schedule in Israel. In that year the incidence rate of measles was 29 per 100,000 due to an outbreak, and declined gradually to 1.7 per 100,000 in 2004 [26] [Figure 1].

There are still occasional out-

breaks of measles in Israel among populations that refuse immunizations and other hard-to-reach populations. The fact that these difficult-to-reach populations can achieve high rates of immunization coverage for measles vaccine is supported by data from Israel documenting the success of a targeted program to improve immunization coverage among semi-nomadic Bedouin [27].

Measles outbreaks occur periodically so that reported annual incidence rates may not accurately reflect the susceptibility of the population. In Israel, the introduction of the measles immunization (one-dose) in 1967 and the second dose policy in 1990 were associated not only with a reduction in annual incidence rates of measles, but also with a reduction in the frequency and severity of outbreaks [Figure 1].

Two outbreaks among the ultra-Orthodox Jewish population in the Jerusalem area occurred in 2003–2004, in which the incidence rate of measles in neighborhoods with outbreaks was 272.9/100 000 children aged 0–14 years, as reported by Stein-Zamir et al [28]. This population has a high rate of refusal of routine immunizations. Although immunization coverage against measles was 88.3% at age 2 years for children who were born in 2000, an outbreak still occurred [28]. This shows the importance of maintaining high immunization coverage for both first and second doses of measles vaccine in order to prevent outbreaks of measles [28,29].

Israel is currently in the midst of an outbreak of measles concentrated in the ultra-Orthodox population of Jerusalem due to a case imported to the country via an ultra-Orthodox man from England who flew to Israel while in the incubation period of measles. In the current outbreak, Stein-Zamir and co-authors reported that 491 cases of measles occurred in Jerusalem from August 2007 to 8 January 2008. The vast majority of cases occurred in the ultra-Orthodox Jewish population, among those who do not immunize their children [30]. Cases have now been

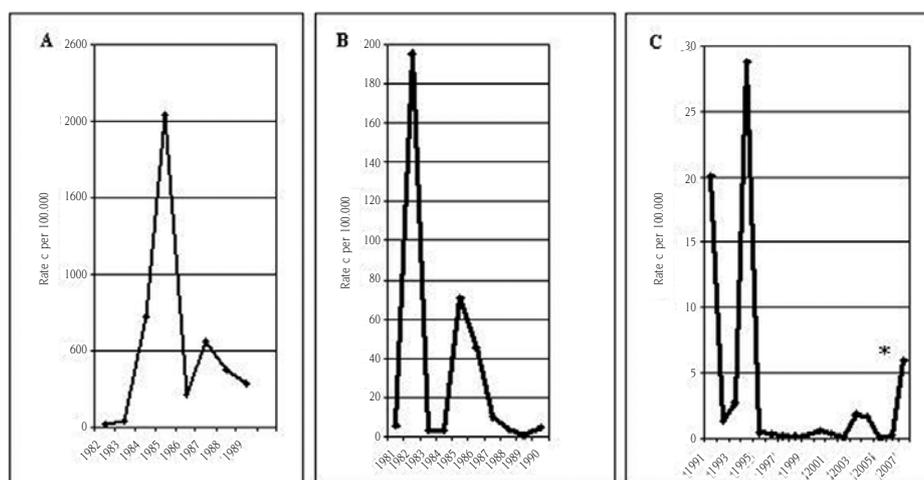


Figure 1. Measles. Rates per 100,000. [A] 1951–1959, [B] 1981–1990, [C] 1991–2007. Source: ICDC Department of Epidemiology. Notifiable Infectious Diseases in Israel. 54 years of surveillance. 1951–2004. 2006; publication No 245. * 2005–2007: Data of Department of Epidemiology, Ministry of Health, Israel, 2007.

reported in other districts of Israel, primarily among the ultra-Orthodox. The national incidence rate of measles in Israel for 2007 was 6.0/100,000 [31]. This rate is much lower than that of the previous major outbreak in Israel in 1994 in which the national incidence rate was 28.4/100,000 [32]. This illustrates the success of the two-dose policy along with the importance of continuous outreach programs to improve immunization coverage among hard-to-reach populations.

Summary

The data presented above show that most countries of the Middle East (Israel and countries of the Eastern Mediterranean Region of the WHO) are progressing towards achieving WHO goals for improving immunization coverage for measles immunization to over 90%, along with the introduction of a two-dose immunization strategy. There has been corresponding progress in the reduction of incidence of measles. However, the goal of the WHO to eliminate measles has not been achieved and is unlikely to be in the near future.

The current outbreak of measles in Israel shows that in an era of globalization, regional programs to eliminate measles with a two-dose strategy cannot succeed as long as there are pockets of under-immunized populations in other regions.

Some states in the Middle East (such as Somalia) currently have the status of "failed states" with a disintegration of central government, including preventive health care services. It is not surprising, therefore, that Somalia has a one-dose measles immunization program (at 9 months of age) and that the immunization coverage at that age is only 35%. They have a correspondingly high incidence rate of measles [Tables 1 and 2].

Other countries, such as Israel, that meet all the WHO goals for immunization coverage as well as a two-dose immunization policy, still have periodic outbreaks due to pockets of unimmunized populations. The current measles outbreak in Israel started with a case of measles imported to the ultra-Orthodox population of Jerusalem via an unimmunized man who is a member of the ultra-Orthodox population in England. This shows that regional programs to eliminate measles cannot succeed as long as there are pockets of under-immunized populations in other regions in an era of globalization and rapid transport from one region to another.

The reduction of measles incidence requires functioning states with strong preventive health care services, along with continuous outreach programs to reach pockets of unimmunized populations. The maintenance and strengthening of preventive health care services in Israel, including preventive child health care services

in Maternal and Child Health stations ("Tipat Halav") as well as school health services, are critical in order to maintain the achievements in Israel and progress towards reducing the incidence of measles in Israel as well as decreasing the frequency and severity of outbreaks.

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