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

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Key words: measles, immune response, immunization coverage, two-dose measles immunization, measles elimination

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

\textsuperscript{MMR = measles-mumps-rubella} 
\textsuperscript{lg = 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.

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<tbody>
<tr>
<td>Israel</td>
<td>91</td>
<td>94</td>
<td>96</td>
<td>12 mos; 6 yrs</td>
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<tr>
<td>Afghanistan</td>
<td>20</td>
<td>35</td>
<td>64</td>
<td>9 mos; 18 mos</td>
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<td>Bahrain</td>
<td>87</td>
<td>98</td>
<td>100</td>
<td>1.5, 12 yrs</td>
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<td>85</td>
<td>50</td>
<td>65</td>
<td>9 mos; 24 mos</td>
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<td>87</td>
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<td>9 mos; 18 mos</td>
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<td>99</td>
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<td>12 mos; 4-6 yrs</td>
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<td>93</td>
<td>85</td>
<td>9 mos; 15 mos; 6 yrs</td>
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<td>9, 18 mos</td>
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<td>93</td>
<td>97</td>
<td>9 mos; 6 yrs</td>
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<td>Oman</td>
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<td>99</td>
<td>98</td>
<td>12 mos; 18 mos</td>
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<td>Pakistan</td>
<td>76</td>
<td>75</td>
<td>79</td>
<td>9 mos</td>
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<td>Qatar</td>
<td>79</td>
<td>91</td>
<td>100</td>
<td>12 mos; 4-6 yrs</td>
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<td>Saudi Arabia</td>
<td>88</td>
<td>94</td>
<td>97</td>
<td>1, 4-6 yrs</td>
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<tr>
<td>Somalia</td>
<td>30</td>
<td>35</td>
<td>35</td>
<td>9 mos</td>
</tr>
<tr>
<td>Sudan</td>
<td>57</td>
<td>60</td>
<td>73</td>
<td>9 mos</td>
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<td>Syria</td>
<td>87</td>
<td>94</td>
<td>98</td>
<td>10 mos; 15 mos</td>
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<td>Tunisia</td>
<td>85</td>
<td>92</td>
<td>96</td>
<td>15 mos; 6 yrs; 12 yrs</td>
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<tr>
<td>United Arab Emirates</td>
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<td>94</td>
<td>92</td>
<td>9 mos; 15 mos; 6 yrs</td>
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<tr>
<td>Yemen</td>
<td>74</td>
<td>71</td>
<td>76</td>
<td>9, 18 mos</td>
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</tbody>
</table>

NA = data not available

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...
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 [19,20]. The current immunization policy of Saudi Arabia is a three-dose strategy (9 months, 12 months, 4–6 years). Removal of a dose in children older than 12 months [20,24]. The current immunization policy of 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 15.67/100,000 in 2005 [21].

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 migrant and nomadic populations [23].

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

<table>
<thead>
<tr>
<th>Country</th>
<th>1990 Incidence/100,000</th>
<th>2000 Incidence/100,000</th>
<th>2005 Incidence/100,000</th>
</tr>
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<tbody>
<tr>
<td>Israel</td>
<td>5.1</td>
<td>0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>11.0</td>
<td>27.5</td>
<td>43</td>
</tr>
<tr>
<td>Bahrain</td>
<td>11.9</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Djibouti</td>
<td>18.6</td>
<td>25.6</td>
<td>37.6</td>
</tr>
<tr>
<td>Egypt</td>
<td>1.6</td>
<td>3.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Iran</td>
<td>9.4</td>
<td>17.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Iraq</td>
<td>16.5</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Jordan</td>
<td>8.9</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Kuwait</td>
<td>3.31</td>
<td>0.27</td>
<td>0.37</td>
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<td>Lebanon</td>
<td>NA</td>
<td>0.15</td>
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<td>21.48</td>
<td>NA</td>
<td>498</td>
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<td>Morocco</td>
<td>6.39</td>
<td>25.2</td>
<td>20.6*</td>
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<td>Oman</td>
<td>68.5</td>
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<td>0.97</td>
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<td>19.5</td>
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<td>0.7</td>
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<td>56.54</td>
<td>150.7*</td>
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<td>6.66</td>
<td>0.49</td>
<td>0.14</td>
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<tr>
<td>United Arab Emirates</td>
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</tr>
<tr>
<td>Yemen</td>
<td>NA</td>
<td>2.62</td>
<td>29.96</td>
</tr>
<tr>
<td>All countries</td>
<td>15.67</td>
<td>7.98</td>
<td>2.8</td>
</tr>
</tbody>
</table>

NA = data not available.
* 2004 rate

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 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 outbreaks 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].

Source: ICDC Department of Epidemiology. Notifiable Infectious Diseases in Israel. 54 years of surveillance. 1951–2004. 2006; publication No 245.
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.

References


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Capsule

Simultaneous brain imaging and microstimulation

Until now, functional brain-imaging studies have focused on how regions are activated by a particular stimulus or cognitive task. However, how nodes within a functional network causally interact with each other is still poorly understood. Ekstrom and collaborators used a novel combination of chronic intracortical microstimulation and functional magnetic resonance imaging in awake, behaving monkeys to study the impact of frontal top-down signals on incoming sensory information. Frontal eye fields could modulate early visual areas only in the presence of a visual stimulus, whereas higher-order visual areas could be modulated independent of visual stimulation.

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Eitan Israeli

Capsule

Celiac disease autoantibodies in severe autoimmune liver disease, and liver transplantation

Celiac disease (CD) is a gluten-sensitive enteropathy caused by an inappropriate immune response to ingested wheat gluten proteins and related proteins in barley and rye. CD is strongly associated with HLA DQ2 and DQ8 and with the presence of anti-endomysial (EMA) and anti-transglutaminase (TTG) antibodies. The clinical presentations of CD may vary from silent disease to classical malabsorption with extraintestinal manifestations. The association between liver disease and CD is well documented and liver abnormalities are present in 40–50% of CD patients, whereas prior liver disease is associated with a four to sixfold increased risk of latent CD. In a recent study Rubio-Tapia et al. investigated 488 pre-transplantation patients with end-stage liver disease, of whom 310 had end-stage autoimmune liver disease (ESALD) and 178 non-autoimmune disease. Serological evidence of CD was documented in 3% and 0.6% of patients with ESALD and non-autoimmune liver disease respectively. The prevalence of anti-TTG and anti-EMA antibodies were significantly higher in patients with HLA DQ2 or DQ8 haplotypes. Anti-TTG and anti-EMA normalized in 94% and 100% of patients 12–24 months after liver transplantation without gluten withdrawal from their diet, however among the patients with classical CD two patients developed intestinal lymphoma 8 and 9 years post-transplantation. Thus, patients with ESALD, especially those with HLA DQ2 or DQ8, had a high prevalence of CD-associated antibodies, and although immune suppression may decrease the presence of CD-associated autoantibodies and ameliorate symptoms of CD, it might not be enough to prevent the development of intestinal lymphoma.

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Nancy Agmon-Levin