Measles in Saudi Arabia: from control to elimination

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This article describes the tremendous efforts made in the field of measles immunization in Saudi Arabia in the past 20 years, from the control phase to the elimination phase. Mandatory measles vaccination with one-dose Schwartz vaccine was introduced in 1982 by a royal decree, a step aimed at increasing vaccine coverage. In 1991, a two-dose schedule was implemented using Edmonston-Zagreb measles vaccine , with a first dose at 6 months to protect children younger than 9 months and a second dose of MMR at 12 months of age to protect those who did not respond to the first dose. A marked reduction in the epidemic peak and a shift of infection to older age were noticed. But the same data showed that 50% of measles cases in the 1- to 4-year age group occurred in vaccinated children. In 1998, with the start of elimination phase, an MMR campaign was launched in two phases, targeting school children in 1998 (secondary schools) and in 2000 (primary and intermediate schools). Evaluation of the MMR campaign and surveillance data was reflected in the measles immunization policy by shifting the age of measles immunization to 12 months and to preschool using the two-dose MMR schedule.

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Tremendous efforts have been made in the field of immunization in Saudi Arabia in the past 20 years. The introduction of measles vaccination into immunization programmes has resulted in a marked reduction in the incidence of the disease and its associated morbidity and mortality. However, the shift from immunity acquired through natural exposure to immunity induced through vaccination is a delicate and complex process that needs continuous monitoring and evaluation. Despite the remarkable progress made in measles control with the introduction of measles vaccination, sustained political and economic commitments are needed because outbreaks continue to occur, even in highly vaccinated populations. This continuous strain on resources was the most important factor that has changed the concept of measles prevention and control in all countries, from a strategy of control to one with an ultimate aim of elimination, and then global eradication. In this article, we provide an update on efforts to develop an immunization strategy against measles in Saudi Arabia. We also describe the effect of the level of intervention on the disease pattern.

Pre-vaccination Era

In the pre-vaccination era, all children in Saudi Arabia, as in any developing country, were immune to measles by the age of 5 years, but measles-related mortality was much higher in those days.[1] Once the disease was introduced, the high secondary attack rate characteristic of the measles virus meant that transmission continued relentlessly until the proportion of susceptible individuals fell to 3% to 7%. The epidemic

then ceased until a pool of susceptibles formed again, mainly from a new cohort of younger children who had lost their maternal antibodies.[2,3]

Lessons Learned From Other Countries

In the early years of measles vaccination in developed countries, morbidity and mortality were greatly reduced once adequate coverage was provided. But after this initial success, reported cases of measles in the USA increased 6 to 9 fold in the period 1989-1990 over the previous rate for the period 1985-1988.[4] This resurgence of cases was a result of the accumulation of unvaccinated susceptible children and children who had vaccine failure. A decline in circulating wild virus, which can play an important role in maintaining protective post-vaccination levels of antibody,[5] may have contributed to this resurgence. Accordingly, a decrease in the circulating wild virus should be compensated through additional doses of vaccine. These changes are consistent with the characteristics of the control phase. As vaccine coverage improves, the proportion of cases with history of vaccination increases.[6]

Control Phase

Introduction of Measles Vaccine in Saudi Arabia

Mandatory measles vaccination with the one-dose Schwartz vaccine was introduced in Saudi Arabia in 1982 by royal decree. Although measles vaccination started in 1974 for children aged 1-9 years, measles vaccination became a requirement for obtaining a birth certificate in 1982, a step aimed to increase the coverage rate. Accordingly, the coverage rate increased from 8% in 1980 to 80% in 1984 and to more than 90% in 1990.[7] Although this was accompanied by a remarkable decrease in measles incidence (Figure 1), the overall impact of measles immunization was unsatisfactory. A substantial number of cases were still occurring in children younger than 9 months, and measles infection shifted to older age groups, with a large proportion of cases occurring in vaccinated children.[8] Epidemics were still occurring, but with a lower epidemic peak and a longer inter-epidemic period. A follow-up study for measles maternal antibody showed that 33% of children at 6 months of age and 36% at 9 months of age were negative for measles maternal antibody.[9] Assessment of seroconversion after Schwartz measles vaccination at 9 months showed that only 65% had a fourfold rise after immunization. After more than 10 years of using the Schwartz measles vaccine in Saudi Arabia, there was a need for change.[10]

Edmonston-Zagreb Measles Vaccine and the Two-dose Schedule in the 90s

The first task in planning the new measles immunization policy was to solve the problem of primary measles vaccine failure due to persistent maternal antibody. Advancing the age of measles immunization from 9 to 6 months to protect children younger than 9 months was a second objective. A clinical trial was done to compare the immunogenicity of a standard dose of Edmonston-Zagreb (E-Z) with the Schwartz measles vaccine at 6 months of age.[11] Children vaccinated with E-Z at 6 months showed a seroconversion of 96% (26/27) compared with 65% (18/28) in children vaccinated with Schwartz at 6 months and 69% (20/29) in children vaccinated with Schwartz at 9 months of age. To verify this result a follow-up study was done to evaluate the pattern of measles antibody after E-Z immunization in Saudi infants. The geometric mean antibody titre (GMT) of measles antibody increased from 79 mIU/mL, two months after E-Z immunization at 6 months of age, to 222 mIU/mL, 9 months after immunization (P=0.0001).[12] This phenomena was described by Sabin as a delayed seroconversion.[13] The use of a standard dose of E-Z at 6 months of age was included in a two-dose vaccination policy as part of a measles elimination strategy, where the measles-mumps-rubella (MMR) vaccine was given at the age of 12 months. This policy was implemented in 1991. Although MMR was given before on a non-compulsory basis, its inclusion as a part of the Extended Program of Immunization (EPI) and as a requirement for obtaining a birth certificate, resulted in an increase in MMR coverage from below 20% before 1991 to more than 90% in 1993.

The impact of implementing the two-dose schedule and maintaining a high coverage of more than 90% was reflected on the epidemiological pattern of measles in Saudi Arabia (Figure 2). National surveillance data showed that the percentage of cases among children over 15 years of age increased from 10% in 1987 to >40% in 1997, whereas the percentage of cases among the 1- to 4-year age group dropped by 20%. The percentage among 5- to 14-year olds dropped by 10%.[7]

A marked reduction in the epidemic peak was noticed, from 500/100 000 in the 1970s to less than 80/100 000 in the 1990s. The incidence among

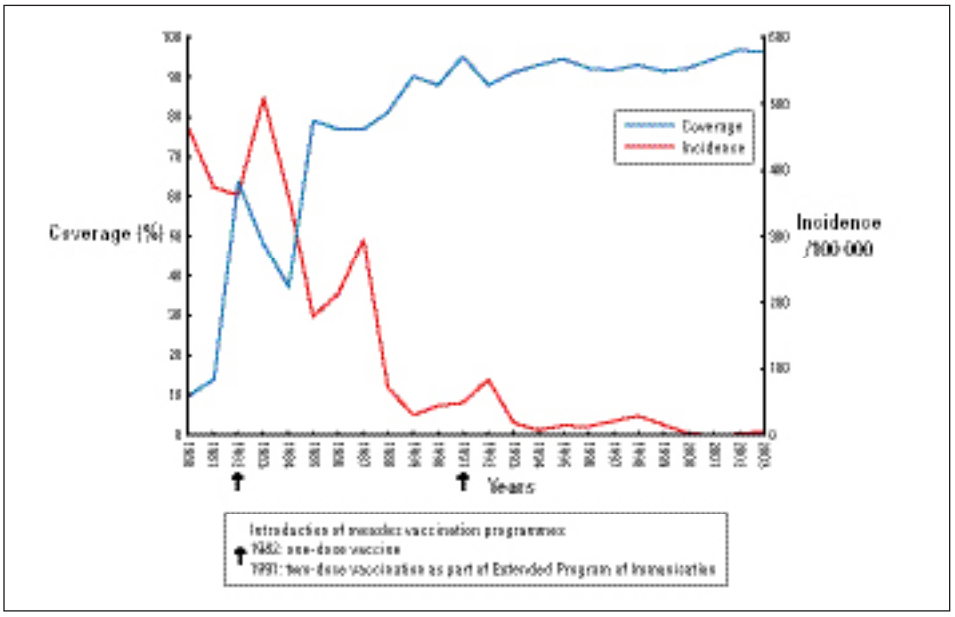

Figure 1.
Measles incidence and vaccination coverage in Saudi Arabia, 1980-2002, based on national surveillance data and Saudi demographic data provided by the statistics department of the Ministry of Health.

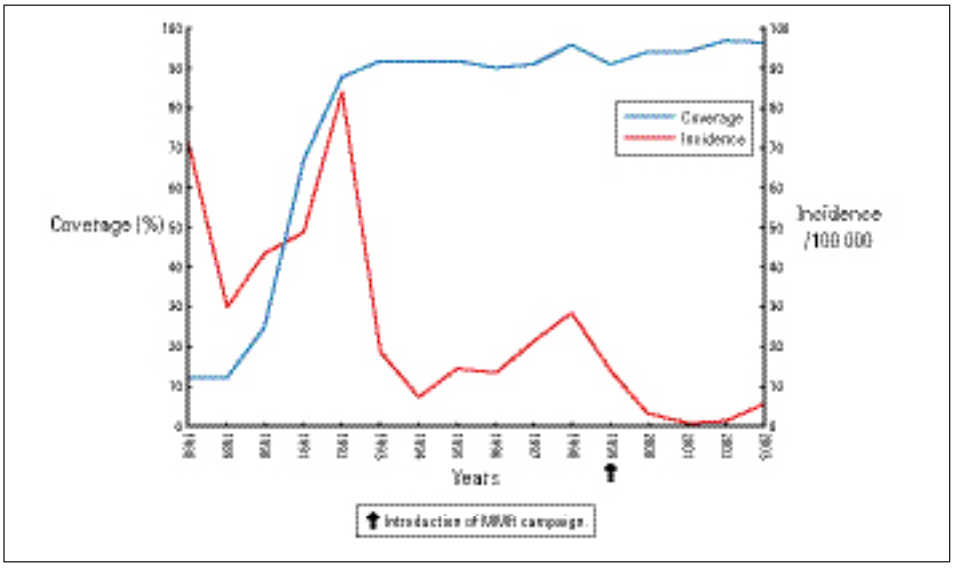

Figure 2.
The effect of using the MMR vaccine as a second dose in measles vaccination, based on national surveillance data and Saudi demographic data provided by the statistics department of the Ministry of Health.

children 6- to 8-months old dropped from >400 per 100 000 before implementation of the new policy to <100 per 100 000 in 1997. In 9- to 11-month olds, the incidence dropped from >200 per 100 000 before the implementation of the new policy to <100 per 100 000 in 1997.[7] But the same surveillance data showed that 50% of measles cases in the 1- to 4-year age group were in vaccinated children, compared with 13% in vaccinated children in those older than 15 years and 20% to 40% in the 5- to 14-year age group. This can be explained, at least partially, by the high vaccination coverage in children younger than 5 years of age, and the therefore higher number of cases of vaccine failure among susceptible children compared with unvaccinated children. The percentage of measles in vaccinated children in relation to the total number of measles cases was 52% according to a survey done in the USA.[14] The situation is different in older age groups where cases occur mainly in unvaccinated children or in children who had only one measles dose.

To serologically evaluate the protective effect of the two-dose vaccine 5 years after implementing the new policy, sera were collected before and two

months after MMR at 12 months of age.[15] Before giving MMR at 12 months, 80% of children were seropositive for measles antibody after taking the E-Z vaccine at 6 months of age, but only 60% had a protective level (≥255 mIU/mL). As expected, the antibody level after the first measles dose was lower compared to the early years of implementing the two-dose schedule. This can be explained by the decreased natural exposure to measles infection, which acts as a natural boosting to post-immunization antibody.[5]

After giving the MMR dose, 100% became positive and >95% had the protective level for measles. Only 70% had seroconversion after MMR. Seroconversion was defined as ≥4-fold increase in the antibody titre from the pre-vaccination titre, or a seropostive titre compared to a seronegative pre-vaccination titre. This low seroconversion rate can be explained by the high pre-vaccination positive rate and was proved by the negative correlation between residual pre-immunization titres and the corresponding titre increase after immunization (r=-0.79).[15] This study showed that the effect of the second measles dose (MMR) was excellent at least in the short term. But the persistence of antibody in the long term was not guaranteed. This was evident by the relatively low seroconversion and the negative correlation between pre- and post-vaccination antibody. Also, the decreased incidence of measles has a negative effect on the persistence of post-vaccination antibody.

Elimination Phase

The cornerstones of measles elimination program are the strengthening of routine and supplementary immunization activities and enhancing surveillance activities and laboratory confirmation of reported measles cases. Immunizations activities and surveillance started in 1998 in Saudi Arabia, but laboratory confirmation did not start until 2001.

MMR Campaign in Schools in 1998-2000

Part of the strategy of the elimination phase was an MMR campaign targeting school age children. The purpose of the campaign was to maintain the number of susceptible individuals in the population below the critical number required to sustain transmission of measles virus in 1998-2000. All school children (>4 million) in Saudi Arabia were vaccinated. The campaign was conducted in two phases. The first phase was conducted in September-October 1998 and included all children (1 691 275 children) in the preparatory and secondary schools. The coverage rate was 96.4%. The second phase was conducted in January-February 2000 and included children in primary school in addition to the first year of preparatory school (2 496 613 children). The coverage rate was 96.6%.

The main objective of the campaign was to prevent a predicted epidemic in school age children by vaccinating children who were not vaccinated and vaccinating those with primary or possible secondary vaccine failure. Another purpose was to reduce the high level of susceptibility to rubella and thus reduce the risk of congenital rubella, as many children, especially older children, had not been given rubella vaccine.[16,17]

During the second phase of campaign, in 2002, pre-and post-campaign samples were collected to evaluate the immune response to the MMR given in the campaign. It was interesting to find that the pre-vaccination positivity rate (GMT) of the first-grade children, measured by enzyme-linked immunoabsorbent assay (ELISA), was significantly lower than in children in the sixth grade. This finding was supported by surveillance system data, which showed that the proportion of measles cases was greater in the age group 1 to 5 years.[7] Children in the first grade were previously vaccinated with E-Z measles vaccine at 6 months and MMR at 12 months, while children in the sixth grade were vaccinated according to the old immunization schedule of one measles dose at 9 months with or without MMR, in between 2 to 5 years of age.[18] After the campaign, the protection rate reached almost 100%. Evaluation of campaign data together with surveillance information is an important step to optimize the measles immunization schedule. Also, to optimize the immune response to measles vaccination a rapid increase in coverage of school children from 6 years up to 17-18 years is an important step if a measles immunization schedule is to be shifted to a higher age group. The use of two MMR-dose schedules with the first dose at 12 months and the second dose at pre-school age was implemented in 2001. The first dose is being given after nearly complete waning of all measles maternal antibody. The second dose is given after a reasonable interval to prevent any interference from high levels of post-vaccination antibody. To assure the success of this policy, the coverage level should exceed 90% for both doses and the surveillance system should be strengthened.

Follow-up Campaign for Children in the First to Third Grade Primary Schools

In 2002, a national serosurvey, supported by surveillance system data, showed that there was a window of

susceptibility to measles infection in children in the first to third grades in primary school.[19] Accordingly, a follow-up campaign with MMR was conducted in 2003 targeting that age group.

The success story of polio eradication in Saudi Arabia can be replicated in the case of measles by applying the same scientific approach and by political commitment at all levels.

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References

1. Hedrickse RG, Barr DGD, Mathews TS. Paediatrics in the Tropics. Oxford: *Blackwell Scientific* 1991;592-6.
2. De Quadros CA, Olive JM, Hersh BS. Measles elimination in the Americas: evolving strategies. *JAMA.* 1996;275:224-9.
3. Omer MI. Measles: a disease that has to be eradicated. *Annals of Tropical Paediatrics.* 1999;19:125-134.
4. Forest JM, Burgess MA. Update on immunization. *Curr Opin Pediatr.* 1996;8:21-7.
5. Matter L, Germann D, Bally F, Schopfer K. Age-stratified seroprevalence of measles, mumps and rubella (MMR) virus infections in Switzerlan after the introduction of MMR mass vaccination. *Eur J Epidemiol.* 1997;13(1):61-6.
6. WHO. WHO guidelines for epidemic preparedness and response to measles our breaks. *WHO/CDS/CSR/ISR/99.1.* Geneva May 1999.
7. Al-Mazrou YY, Al-Jeffri M, Ahmed OM, Aziz MS, Mishkas AH. Measles immunization :Early two-dose experience. *Journal of Tropical Pediatrics.* 1999;45:98-104
8. Abanamy A, Khalil M, Salman H, Abdulazeem M. Measles vaccine failure. *Annals of Saudi Medicine.* 1991;11:311-314
9. Abanamy A, Khalil M, Salaman H, Abdulazeem M. Follow-up study for measles maternal antibodies and seroconversion after measles vaccination. *Annals of Saudi Medicine.* 1991;11:51-53
10. Khalil MKM, Al-Mazrou YY, Al-Jeffri M, Al-Ghamdy YS. Measle immunization in Saudi Arabia: the need for change. *Eastern Mediterranean Health J.* 2001;7:829-834
11. .Khalil M. The use of standard dose (3.0 log10 of Edmonston-Zagreb measles vaccine in solving the problem of measles vaccine failure. Annual Scientific meeting of Egyptian Medical Syndicate (EMS). Cairo 2-4 Febraury 1993. No. 43.
12. Khalil M. Follow-up study of children vaccinated against measles at the age of six months with 3.0 log10 Edmonston-Zagreb. *Saudi Medical Journal.* 1993;14(1): 44-45
13. Sabin AA, Arechiga AF, De Castro. Successful immunization of infants with or without maternal antibody by aerosolized measles vaccine (part II). *JAMA.* 1984;251:2363-2371.
14. Center for Disease Control. Measles vaccine efficacy. United States (Editorial). *MMWR.* 1980;29/30:470-2
15. Khalil M, Poltera AA, Al-Howasi M, Herzog C, Gerik E, Wegmuller B, Gluck R. Response to measles revaccination among toddlers in Saudi Arabia by the use of two different trivalent measles-mumps-rubella vaccine. *Transaction of the Royal Society of Tropical Medicine and Hygiene.* 1999;214-219
16. Miller E, Waight P, Gay N, Ramsay M, Vurdien J, Morgan-Capner P, Hesketh L, et al. The epidemiology of Rubella in England and Wales before and after the 1994 measles and rubella vaccination campaign: fourth joint report from the PHLS and National Congenital Rubella Surveillance Programme. *Commun Dis Rep.* CDR Rev 1997 Feb 7;7(2):R26-32
17. Mansour O, Blakely T, Baker M, Tobias M, Bloomfield A. A measles epidemic controlled by immunization. *N Z Med J.* 1998;111(1079):467-71
18. Al-Mazrou Y, Khalil M, Tumsah S, AlGhamdi Y, Al-Jeffri M, Tischer A, et al.Sero-response to measles-mumps-rubella vaccine campaign in Saudi Arabia. *Saudi Med J.* 2002;23(6):680-683.
19. Al-Mazrou Y, AL-Jeffri M, Khalil M, Alghamdi Y, Mishkais A, Bakhsh M, et al. *Serosurvey of diseases targeted by the Expanded Program of Immunization: first part, measles, mumps and rubella.* MoH, 2004. King Fahad National Library Cataloging. LDN 1425/6252.