

Review

Measles immunization in Saudi Arabia: the need for change

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SUMMARY This paper describes the measles immunization programme in Saudi Arabia and the change from the single-dose schedule with the Schwartz vaccine to the double-dose schedule with the Edmonston-Zagreb vaccine. The recent measles-mumps-rubella school campaign is also described.

Introduction

Vaccination is an intervention which affects the natural ecology of infectious diseases such as measles. Shifting from immunity acquired through natural exposure to disease to immunity induced through vaccination is a delicate and complex process requiring continuous monitoring and evaluation.

Prior to the era of universal vaccination, children in developing countries generally acquired immunity to measles if they survived to 5 years of age [1]. This was so because once the disease was introduced, the high secondary attack rate meant transmission would continue relentlessly until the proportion of those susceptible to the disease (susceptibles) fell to between 3% and 7%. The epidemic would then cease until a new pool of susceptibles formed, usually from infants who had lost their maternal antibodies [2,3].

The early years of an initial measles vaccination campaign are usually characterized, if adequate coverage is provided, by significant reductions in morbidity and

mortality due to the disease. In the United States of America (USA), for example, the number of reported measles cases before 1963, when the measles vaccine was registered, was 400 000. By 1997, this number had fallen to 198. Progress towards eradication is, however, not always consistent. There was a six- to ninefold increase in reported cases of measles in the USA during the period 1989–90, compared to the rate for the period 1985–88 [4]. The resurgence of cases is often the result of the accumulation of unvaccinated susceptible children, and of children with vaccine failure. It is now known that circulating wild virus can also play an important role in maintaining post-vaccination protective antibody levels [5]. Accordingly, a decrease in circulating wild virus should be compensated for by additional doses of vaccine. Maintaining this balance requires an ongoing strong political commitment and continued vigilance in vaccination and surveillance. For measles, eradication is the most rational method of preventing infection.

This paper reviews the process of developing an immunization strategy for mea-

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Received: 23/00/00, accepted: 15/02/01

sles in Saudi Arabia, and the effects of intervention on the pattern of disease.

The single-dose schedule: the Schwartz vaccine

Since 1974, a measles vaccine has been in use in Saudi Arabia for children aged 1–9 years. In 1982, to increase coverage rates, measles vaccination became a requirement for obtaining a newborn's birth certificate. Consequently, coverage increased from 8% in 1980 to 80% in 1984, and to > 90% in 1990. The Schwartz measles vaccine was used for this purpose, and although a remarkable decrease in measles incidence in general ensued, the overall impact of immunization remained unsatisfactory. A substantial number of cases continued to occur in children aged < 9 months, and infection also shifted to older age groups, with a large proportion of cases occurring in children already vaccinated [6]. Epidemics continued to occur, albeit with lower epidemic peaks and longer periods between epidemics. Follow-up studies of measles maternal antibody levels showed 33% of infants at 6 months of age, and 36% at 9 months of age to be negative for measles maternal antibodies. Seroconversion after Schwartz measles vaccine of infants at age 9 months showed that only 65% had a fourfold rise in antibody levels after immunization [7]. These results suggested that after more than 10 years of using the Schwartz measles vaccine in Saudi Arabia, there was a need for change.

The double-dose schedule: the Edmonston–Zagreb vaccine

Change came in the form of a new immunization policy, the principal aim of which

was to solve the problem of primary measles vaccine failure due to the persistence of maternal antibodies. Advancing the age of vaccination from 9 months of age to 6 months to protect children aged < 9 months, was a second objective. A clinical trial was carried out to compare immunogenicity of a standard dose of the Edmonston–Zagreb (E–Z) and Schwartz measles vaccines at 6 months of age. Children vaccinated with E–Z at 6 months showed a seroconversion rate of 96% (26 of the 27 children vaccinated), compared to 65% (18 of 28) vaccinated with Schwartz at 6 months, and 69% (20 of 29) vaccinated with Schwartz at 9 months [8].

To verify the results, a follow-up study was undertaken to evaluate the pattern of measles antibodies after E–Z immunization in Saudi infants. Interestingly, the geometric mean antibody titre (GMT) of measles antibody increased from 79 within 2 months after E–Z immunization at 6 months of age, to 222 at 9 months after immunization ($P = 0.0001$) [9]. This phenomenon was described by Sabin as delayed seroconversion [10]. The use of a standard dose of E–Z at 6 months of age was included in a two-dose policy as part of a measles elimination strategy where triple antigen measles, mumps and rubella (MMR) vaccine was given at the age of 12 months. This policy was implemented in 1991. Although MMR had previously been available on a non-compulsory basis, its inclusion as a part of the Expanded Programme on Immunization (EPI), and as a requirement for obtaining the child's birth certificate, resulted in an increase in the rate of MMR coverage from < 20% prior to 1991 to > 90% in 1993.

The impact of implementing the two-dose schedule and maintaining coverage of > 90% is reflected in the epidemiological

pattern of measles in Saudi Arabia. National surveillance data were used to show the epidemiological pattern. Incidence per 100 000 population/year and coverage were determined using Saudi demographic data provided by the Ministry of Health, Department of Statistics. The national surveillance data showed that as a percentage of the total, cases in the age group > 15 years increased from 10% in 1987 to > 40% in 1997, whereas in the 1–4 and 5–14 years age groups, there was a 20% and 10% fall respectively.

There was a marked reduction in the epidemic peak from 500/100 000 in the 1970s to < 80/100 000 in the 1990s. Incidence among children 6–8 months of age fell from > 400/100 000 before the implementation of the new policy to < 100/100 000 in 1997. Similarly, among children aged 9–11 months, the number of cases fell from > 200/100 000 before the implementation of the new policy to < 100/100 000 in 1997 [11]. The same surveillance data also showed that 50% of measles cases in the 1–4 years age group were in vaccinated children, compared to 13% and 20%–40% in > 15 years and 5–14 years age groups respectively. This can be explained, at least partially, by the high vaccination coverage in children < 5 years of age, as the proportion of cases of vaccine failure can increase among susceptible children compared to unvaccinated children. One survey in the USA found the percentage of measles in vaccinated children in relation to the total number of measles cases to be 52% [12]. The high percentage might be expected in that country, where vaccination programmes have been in existence for longer than elsewhere. The above percentage does not reflect vaccine efficacy.

Vaccine efficacy (VE) can be calculated from the following equation [13]:

$$VE = \frac{\text{Unvaccinated attack rate} - \text{vaccinated attack rate}}{\text{Unvaccinated attack rate}}$$

From the above equation, and if the vaccine efficacy is known or replaced by the proportion of children with protective levels, the percentage of measles in vaccinated children can be calculated as follows [14]:

$$PCV = \frac{PPV - (PPV \times VE)}{1 - (PPV \times VE)}$$

where PCV represents the percentage of cases vaccinated and PPV the percentage of the population vaccinated. If we use 95% as the proportion of children with protection and a coverage rate of 90%, the percentage of vaccinated cases should be 30%, which is less than the 50% observed in the surveillance for the 1–4 years age group. This difference can be explained by those children in the 1–4 years age group who received only one measles dose, which lowered the efficacy rate. The situation is different in older age groups, where cases occurred mainly in unvaccinated children, or in children who had received only one measles dose.

To evaluate the protective effect of the two-dose vaccine serologically 5 years after implementing the new policy, sera were collected before and 2 months after the MMR had been given at 12 months of age. Before receiving the MMR at 12 months, 80% of children were seropositive for measles antibodies after taking the E-Z vaccine at 6 months of age and 60% had protective levels (> 255 mIU/mL) before taking MMR at 12 months of age. It is expected that the

antibody level after the first measles dose will be lower compared to the early years of implementing the two-dose schedule. This can be explained by the decrease in natural exposure to measles infection, which serves as a natural boost to post-immunization antibodies [5].

After receiving the MMR dose, 100% of the children became seropositive and > 95% had protective levels for measles. Only 70% had seroconversion after MMR. Seroconversion was defined as a > four-fold increase in the antibody titre from prevaccination titre or seropositive titre compared to seronegative prevaccination titre. This low seroconversion rate can be explained by the high prevaccination positive rate, and was proven by the inverse correlation between residual preimmunization titres and the corresponding titre increase after immunization ($R = -0.79$) [15]. This study showed the effect of the second measles dose (MMR) to be excellent, at least in the short term. But the persistence of antibodies in the long term is not guaranteed. This was evident by the relatively low seroconversion and inverse correlation between pre- and post-vaccination antibodies. Also, the decreased incidence in measles will have a negative effect on the persistence of post-vaccination antibodies.

A decade after the commencement of the two dose schedule, a pool of susceptible children began to accumulate within children of school age — mostly among older children who had never been vaccinated, or who had received only one measles injection, and among younger children in whom the two-dose schedule had failed.

MMR school campaign

In 1998–2000, all schoolchildren in Saudi Arabia (i.e. > 4 million children) were vaccinated. The campaign was conducted in

two phases. The first phase was conducted in September–October 1998, covering children in the preparatory and secondary schools (i.e. almost 1.7 million children). The coverage rate was 96.4%. The second phase was conducted in January–February 2000, to cover all primary-school children, in addition to children in the first year of preparatory school (approximately 2.5 million children). The coverage rate was 96.6%. The main objective of the campaign was to prevent a predicted measles epidemic among school-age children, by vaccinating those previously not vaccinated, as well as those with primary or possible secondary vaccine failure. Another aim 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 previously vaccinated for rubella [16,17].

During the campaign, safety and immunogenicity were assessed, the latter to provide information on the proportion of children with protective levels against the target diseases before and after the campaign. The assessment will also provide baseline data.

During the preparation of this paper, the campaign was at the fieldwork stage. Evaluation of campaign data, together with surveillance information, is important for optimizing the effectiveness of the measles immunization schedule. Also, comprehensive coverage, carried out over a short period of time, of school-age children from age 6 years up to ages 17 or 18 years is an important step if measles immunization is to be shifted for higher age groups. This shift may be needed to optimize the immune response to measles vaccination. The use of the two MMR dose schedule, with the first dose at age 12 months, and the second at pre-school age seems to be a logical option at this stage. The first dose is given after

maternal measles antibodies have waned. The second dose is given after a sufficient interval to prevent any interference from high levels of post-vaccination antibodies.

Analysis of sero-studies from the MMR campaign, in addition to studies to reflect the seroepidemiological situation, should be

carried out first. Immunogenicity trials should also be conducted to evaluate this option before implementing it on a wider scale. In order to ensure the success of the policy, the coverage level should exceed 90% for both doses, and the surveillance system should be strengthened.

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UN agencies launch new plan to halve mortality of measles, a major childhood killer

In a concerted move against one of the world's deadliest childhood diseases, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) announced a new initiative designed to halve global measles deaths by 2005.

Measles accounts for the majority of the estimated 1.6 million annual deaths due to childhood vaccine-preventable diseases. Failure to deliver at least one dose of measles vaccine to all infants remains the primary reason for the high incidence and mortality rates of measles. Under the new initiative, WHO and UNICEF will assist affected countries to:

- Provide a first dose of measles vaccine to *all* infants.
- Guarantee a "second opportunity" for vaccination to increase the probability that as many children as possible are immunized and to assure that those immunized are responding to the vaccination.
- Establish an effective system to monitor coverage and conduct measles surveillance.
- Improve management of complicated measles cases, including vitamin A supplementation.

Source: WHO Press release WHO/16
29 March 2001