

# Reduced Rate of Side Effects Associated with Separate Administration of MMR and DTaP-Hib-IPV Vaccinations

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**ABSTRACT:** **Background:** According to the Israeli immunization schedule, 1 year old babies should receive two concomitant vaccinations: MMR (measles-mumps-rubella), and DTaP-Hib-IPV (diphtheria tetanus acellular pertussis-*Haemophilus influenzae* type b-poliomyelitis). However, about one-third of infants in Israel receive these vaccinations separately. Nurses at a primary care prevention clinic in Israel observed that the separate mode of vaccination is associated with a lower rate of side effects.

**Objectives:** To validate this observation and determine whether it represents an exception or the rule.

**Methods:** A nested prospective follow-up study was conducted in a primary care clinic in Israel. The survey included 191 mothers and their offspring born during 2004/2005. The mothers were interviewed over the telephone 2 weeks after the day of vaccination.

**Results:** The rate of adverse effects in children who received the injections separately was significantly lower than among those who were vaccinated simultaneously (40% vs. 57%).

**Conclusions:** It may be necessary to reconsider the current vaccination policy regarding concomitant injections.

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**KEY WORDS:** measles-mumps-rubella, DTaP-Hib-IPV, vaccinations, adverse effects

Healthy newborn infants are born with all their organ systems already *in situ* at birth. The functional capacity of these systems, however, immune system included, becomes mature and active during the first years of life. During the first few months of its life, the newborn is passively protected from external infections by antibodies that had been transferred to it from the maternal bloodstream through the placenta. With time this protection wanes, leaving the baby to independently cope with potential pathogens. Throughout history, this exposure in early infancy led to countless casualties and handicaps. This changed with Edward Jenner's pioneering observation that a vaccination with the low virulence cowpox virus has the potential to prevent infection with smallpox [1].

In Israel, the current vaccination schedule includes vaccinations against ten diseases [2]. Apart from hepatitis A and B, the national schedule includes vaccinations against polio; diphtheria, tetanus and pertussis; influenza; and mumps, measles and rubella. MMR is scheduled for month 12 of life. Inactivated polio vaccine, DTaP, and Hib (the quintuplet vaccination) are scheduled at months 2, 4 and 6 in the first year of life, with a booster between months 12 and 18. An interval of 6 months should separate between the third injection of the quintuplet vaccination and the fourth. Thus, if the third injection of QV is given on time, at month 6, the fourth injection can be given simultaneously with the first injection of MMR. If there is a delay in the QV injection, it should be given at a later time, separately from the MMR. Thus, current protocol results in either simultaneous or separate administration of these vaccinations.

The model of “simultaneous vaccination” and combination vaccines is commonly used to reduce the number of injections, without compromising the effect [3]. As a result, children's immune systems must cope with the introduction of a number of foreign antigens in a narrow time frame, but the total number of antigens (proteins and polysaccharides) is reduced. Scientists believe that the immune systems of “young infants have an enormous capacity to respond to multiple vaccines, as well as to the many other challenges present in the environment” [4]. MMR is a triple antigen vaccination against measles, mumps and rubella. DTaP is also a triple antigen vaccination against diphtheria, tetanus and pertussis (acellular). Hib is the acronym for the vaccination against *Haemophilus influenzae* type b, and IPV for inactivated polio virus. The combination of these two vaccinations therefore exposes the infant's immune system to an array of eight foreign antigens at the same time.

Scientific data suggest that vaccines are generally safe to administer and have only minor side effects. For example, MMR-related side effects include fever, a mild rash, flu-like symptoms, and the swelling of glands in the cheeks or neck. If they do occur, it is usually within 7–12 days after the injection.

MMR = mumps, measles, rubella  
DTaP = diphtheria-tetanus acellular pertussis  
Hib = *Haemophilus influenzae* type b  
QV = quintuplet vaccination

tion. Other, less common effects include seizures caused by fever, as well as temporary pain and stiffness of joints, temporary low platelet count (which can cause a bleeding disorder), and, very rarely, a serious allergic reaction [5].

DTaP vaccine, a component of DTaP-Hib-IPV, is further associated with common side effects such as fever, redness or swelling, soreness or tenderness at the site of the shot, fussiness, tiredness, poor appetite, and vomiting. These problems generally occur within 1 to 3 days after the injection. Other unusual effects have also been reported, such as seizure, crying non-stop for 3 hours or longer, elevated temperature (above 40.5°C), and, very rarely, a serious allergic reaction [6].

It is plausible that the frequency and severity of adverse effects is related to the number of vaccines (antigens) injected concomitantly, but there is still no evidence of such a connection. Furthermore, there have been reports of a variety of autoimmune manifestations associated with vaccines, but there is still no proof of causality [7].

While it seems fitting to blame the vaccine's antigen as the component responsible for the adverse reaction, the possibility that the symptoms represent a reaction to the adjuvant added to the vaccine should also be considered [8]. The general trend today is to give more vaccines in a single visit. It is believed that this practice will increase both compliance with the vaccination regime and coverage. Multivalent vaccines have the advantages of reduced administration costs, increased coverage, and decreased exposure to vaccine excipient (e.g., gelatin or thimerosal). These substances, in which the vaccine antigen is immersed, are considered to be relatively common causes of vaccine adverse reactions. On the other hand, the increasing complexity of antigen mixtures can make it difficult to determine the cause of the vaccines' adverse effects.

Immunization schedules in many countries do not recommend administration of MMR and QV vaccines simultaneously [Table 1] [9-13]. In Israel, the simultaneous administra-

tion of the QV and MMR depends on the time of the injection of the previous QV. As a result, about one-third of the candidates for these vaccinations receive them separately. This is due to compliance with protocols (51%), delay of the booster vaccination (31%), erroneous calculation of the appropriate date for injection (8%), and maternal discretion (9%).

Nurses at a primary care clinic in the Afula region observed that the mode of separate administration of these vaccines is associated with a lower rate of adverse effects.

## SUBJECTS AND METHODS

A nested prospective follow-up study was conducted in a primary care clinic in Israel and included 191 mothers and their 1 year old babies born in 2004/2005. Data collection was carried out continuously for 3 months in winter and 6 months in the summer. The children were registered in the clinic and received both MMR and DTaP-Hib-IPV vaccines, some simultaneously and some separately.

The participants in our study comprised two groups: 102 randomly selected children who received both vaccines in one day (group A), and 74 children who received the vaccines separately (group B).

Data were collected from the clinic's register, which documented the common practice of staff and patients. No intervention was initiated for the sake of this study. A Helsinki committee approval was therefore irrelevant.

The mothers were interviewed by telephone 2 weeks after the date of vaccination. The mothers of children who were vaccinated on two separate occasions were interviewed twice. The questionnaire was based on the VAERS [14]. VAERS (Vaccine Adverse Event Reporting System) is a 27 item questionnaire used in the United States for reporting adverse events of vaccinations and is commonly used as the "gold standard" in the Lower Galilee area.

The questionnaire includes questions on the infants' personal data (age, gender), health care provider's data, mothers' data, a detailed report of adverse effects in open questions, as well as in a set of closed statements, information about vaccination/s given on that day as well as those given in the preceding 4 weeks, and current and prior medical conditions.

The mothers answered questions on adverse effects that emerged after the shots; they were also asked to provide sociodemographic information including their age, education, ethnic group, marital status, religion, working status, and number of children in the family, and the reason why two separate injections were given. In addition, every mother stated her personal preference regarding the mode of administering the vaccines.

Statistical analysis used protection effect calculations for assessing correlation between mode of vaccination and frequency of side effects. The association between the mothers'

**Table 1.** Comparison of immunization schedules in various countries

Country	Recommended age for DTP/DTaP vaccine (mos)	Recommended age for MMR vaccine (mos)	Vaccines given to 1 year old children according to immunization schedule
USA	2,4,6,15	12-15	HBV, MMR, VAR, PCV
Canada	2,4,6,18	12	MMR, VAR, PCV
Australia	2,4,6 mos and 4 yrs	12	MMR, HBV-Hib, Meningitis
France	2,3,4,18	12	MMR
Germany	3,4,5,24	15	None
United Kingdom	2,3,4 months and 4 years	12	MMR
Finland	3,4,5,20-24	14-18	IPV
Israel	2,4,6,12	12	MMR,DTaP, IPV, Hib

**Table 2.** Adverse effect rates according to the mode of administering vaccines

Administration of vaccines	No. of vaccinated children	No. of adverse effects reports	Rate of adverse effect reports (%)	P value
Simultaneously	102	58	57	*0.0236
Separately	74	28	38	

\* Using the chi-square test.

**Table 3.** Adverse effect rates according to administration mode and the season of year

	No. of vaccinated children	No. of adverse effects reports	Rate of adverse effects reports (%)	P value
Separately in summer	62	24	38.7	
Simultaneously in summer	80	49	61.3	< 0.07
Separately in winter	27	12	44.4	NS
Simultaneously in winter	22	9	40.9	< 0.05

age and their preference of vaccination mode was tested by the Cochran-Armitage trend test.

## RESULTS

The rate of adverse reaction among children who were vaccinated separately was significantly lower than in those who were vaccinated simultaneously: 28 of 74 (37.8%) versus 58 of 102 (56.9),  $P = 0.0236$  [Table 2].

Table 3 depicts the adverse effect rates according to season of the year. Differences in these rates were more accentuated in the summer season: 24 of 62 (38.7%) in the "separate" group compared to 49 of 80 (61.2%) in the "simultaneous" group. In the "winter" group, which constituted only a quarter of the total sample size (49 of 191), the difference was not statistically significant. Indeed, a small insignificant difference in side effects was noted during the winter season in the opposite direction: 12 of 27 (44.4%) in the "separate" group and 9 of 22 (40.9%) in the "simultaneous" group. Significant rates of some specific side effects were noted, such as rash (19.6% in the concomitant group vs. 10.8% in the separate group), diarrhea (12.7% vs. 6.8%), and fever (9.8% vs. 5.4%).

A significant age distribution was also noted: women of 35 years or older preferred the separate mode of vaccination, as compared to women aged 30–34 ( $P = 0.0314$ ).

## DISCUSSION

It is common knowledge that medical interventions intended to heal are not free from adverse effects. When this occurs in

a sick person it is an accepted phenomenon. This is not the case with vaccinations. Vaccinations are given to a healthy person and adverse effects are much less tolerable. Every effort is therefore taken to prevent or lower the rate of side effects of vaccinations.

This study reports the results of injecting children with both MMR and the QV vaccines: some received both of them at one single visit, i.e., simultaneously, while others received them separately. Our results show that the rate of adverse reactions in simultaneously administered vaccines was higher than those given separately. The side effect rates that we found are higher than reported in previous studies [15-17]. It is reasonable to assume that this is attributable to the short time interval between the vaccination and the interview: in our study this time interval was 2 weeks only. In other studies this information is usually collected on the subsequent visit, usually at least one month later, with an increased effect of recall bias [7,10,18]. We also found that 38.7% of the vaccinated children received separate shots, not including 7.9% of the children who received only MMR despite the accepted practice of simultaneous vaccine. For 30.9% this was due to the parents' failure to visit the clinic for the previous shot, which had been scheduled when the child was 6 months old.

Results of previous similar studies were inconsistent: while some found similar rates of adverse effects following either simultaneous or separate injections [19], others found different side effect rates, but with no statistical significance [20-22].

The finding of the adverse reactions rates and the relationship between these and the seasons of the year were interesting and not expected. Reviewing the evidence for seasonal fluctuations of immune function and peaks of infectious disease incidence showed that in some studies seasonal variations of immune function were dependent on an interaction between two factors: the suppression of immune response due to changing energetic conditions and an endogenous rhythm of enhancement of immune response that is dependent on photoperiod, clocks and melatonin. In other words, an expected decrease of immune response is observed during the winter [23].

In the "separate" group, we did not find a correlation between the adverse reaction rates and the time interval between vaccinations (either short – less than 5 weeks, or long – more than 5 weeks) in separate administration. We concluded that a 5 week interval between injections is long enough to assure a reduction in the rate of adverse effects.

A relationship was also found between the number of children in the family and the mothers' reporting of adverse reactions. In families with one or two children who had the simultaneous vaccination, there were significantly 2.98 times more reports than in families with three and more children who received separate injections. It is possible that mothers of many children will either pay less attention to minor side effects or will accept them as a normal response

after a vaccination rather than something to worry about.

Despite the low compliance in answering questions about personal preference on the manner of vaccine administration (69.1%), there was a significant trend of an increased number of women preferring separate injections for their children; this approach was demonstrated among women aged 35 or more as compared to the 30–34 year old group. A possible explanation for this is that younger mothers tend to accept the authority of public health nurses and follow their recommendations, whereas more experienced older mothers do not automatically accept the nurses' instructions and recommendations to the same extent.

This study has certain limitations. Educational framework is obviously a confounding factor. A child who attends a daycare center has a greater chance of becoming infected than one who stays at home. Common symptoms such as high temperature, cough, runny nose, rash, diarrhea, vomiting and poor appetite may indeed be side effects of vaccines, but they may also be symptoms of an acute viral infection. Another limitation is that the study was conducted in a small geographical area and the sample was relatively small and from a uniform population. Generalization of the results of this study requires an increased sample size and a more diverse population. Including participants from a primary care clinic in the Arab sector would allow for better understanding of the relationship between administration mode and the rate of side effects. This was a prospective study with a time limitation. Collecting the data took 8 months to reach the desired sample size. The prospective design of our study was chosen to neutralize participants' recall bias. Usually, mothers are asked about any adverse reactions in the subsequent visit, which may occur one month or more after the vaccination. This long time lapse between the date of injection and the interview may affect the parents' power of recall and their reporting of adverse reactions. Interviewing the mothers over the telephone 2 weeks after the date of vaccination provided a more reliable database. The time limitation of the data collection period probably resulted in a choice bias. Data were collected continuously over 3 months in the winter and 6 months in the summer. As a result, there were almost three times more "summer" children vaccinated than in the winter (142 vs. 49). Another study, conducted for longer than a full year, may show different results or verify those already recorded.

## CONCLUSIONS

In this study it was demonstrated that the rate of adverse effects in the separately vaccinated group was significantly lower than in the simultaneously vaccinated group. The results of this study do not support the national recommendation of simultaneous vaccinations of MMR and DTaP-Hib-IPV. Rather, our data call for reconsideration of the current policy of simultaneous injections of MMR and DTaP-Hib-IPV – at least until a larger study is conducted.

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