IMMUNOGENICITY AND REACTOGENICITY OF INDIGENOUSLY PRODUCED MMR VACCINE

Indra Bhargava
B.C. Chhaparwal
M.A. Phadke
Simin F. Irani
Dheeraj Chhaparwal
Sanjay Dhorje
C.P. Maheshwari

ABSTRACT

Objectives: To study immunogenicity and reactogenicity of indigenously produced MMR vaccine and to assess the booster effect of MMR immunization on measles seroconversion.

Design: A longitudinal follow up.

Setting: Hospital based and home follow up, as required.

Subjects: 89 children already immunized for measles, between 15 to 24 months of age for immunogenic evaluation and 866 subjects for the reactogenic component.

Methods: Prevaccination and postvaccination samples collected one and four weeks after vaccination were studied by ELISA for IgG and IgM antibodies against the three diseases. A clinical follow up of immunized children was done at 3 days, 7 days, 6 weeks and 6 months after immunization.

Results: IgG positivity 4 weeks after immunization rose from 75% to 100% for measles, from 22% to 92% for mumps, and from 13% to 99% for rubella. Only mild side effects including pain and swelling in 37 (4.3%) cases, mild fever in 51 (5.9%) cases, cough in 40 (4.6%) cases and a transient rash in 7 (0.8%) cases were observed.

Measles, mumps and rubella (MMR) related morbidities have declined considerably since the introduction of an effective(1-7) and safe(8,9) MMR vaccine. Recently, two doses of this vaccine have been recommended by the American Academy of Pediatrics(10) and several other workers(11-16) with the assumption that the second dose will result in a better sero-conversion for measles.

An imported MMR vaccine was employed in the country for a considerable period of time. Recently an indigenously manufactured MMR vaccine has also become available. The present study was designed to evaluate the immunogenicity and reactogenicity of this indigenously manufactured MMR vaccine and to ascertain the seroconversion benefit(s), if any, of MMR vaccination in children already immunized for measles.

Conclusions: The indigenously manufactured MMR vaccine has an excellent immunogenicity and low reactogenicity with a booster effect for measles seroconversion in children already immunized for this disease.

Keywords: Measles, Mumps, Rubella, Immunogenicity, Reactogenicity, Side effects, Seroconversion.
Subjects and Methods

This multicentric study was initiated in August 1994 at the M.G.M. Medical College and Chacha Nehru Hospital for Children, Indore; G.S. Medical College and K.E.M. Hospital, Bombay; and B.J. Medical College and Sasoon Hospital, Pune. The study had two components, namely, immunogenicity evaluation and reactogenicity evaluation. A cohort of apparently healthy children 18 to 24 months of age with a history of measles vaccination at 9 months of age, as verified by immunization cards were selected at each centre. An additional 30 children aged 25-36 months were included at the Indore Centre for reactogenicity evaluation. The total number of subjects available for reactogenic and immunogenic components were 866 and 89, respectively. Care was taken to exclude subjects with a history of neurological symptoms and presence of conditions predisposing to neurological dysfunction. These children were administered the indigenously manufactured vaccine- (EZ strain of measles virus, LZ strain of mumps virus and RA 27 strain of rubella virus) by the intramuscular route immediately after reconstitution With the diluent supplied by the manufacturer. The vaccines for each center's requirement were provided as a one time supply, which had been stored at 2-8°C, till used. Appropriate records for the vaccine batch and it's storage were maintained.

For assessing reactogenicity of the vaccine, subjects were evaluated during vaccination and later at 3 days, 7 days, 6 weeks and 6 months intervals. Special features evaluated include local pain and swelling, fever, anaphylaxis, a transient rash, arthralgia or arthritic symptoms, paresthesia, encephalopathy, irritability and discomfort. Adequate care was taken to ensure follow up of the children and preventing dropouts, by not only talking and reassurance to the parents, but also by other incentives as careful medical care, general tonics and persuasion by the paramedical personnel. Completeness of the follow up and prevention of dropouts was ensured by a complete home address of all the subjects and home visits by the workers, for hospital drop outs.

Three blood samples were collected from each child by a trained medical person, for the immunogenic component; before immunization, one week after immunization and six weeks after immunization. Serum was separated from the collected blood and transported to the Serum Institute of India Research Foundation, Pune under appropriate conditions. All the serological tests were carried out by the same team at the laboratories of the Serum Institute of India Research Foundation, Pune. Serum from each center was tested for the presence of IgM and IgG antibodies against measles, mumps and rubella viruses. All the antibody estimations of one kind were performed using ELISA kits from the same company—Virotech, Germany and Diamedix USA. Appropriate negative and positive controls were put up during every testing event.

The adequacy of the statistical power of the study was ascertained from the sample size consideration in the following manner. For the reactogenic component, a sample size of 650 is sufficient to evaluate an expected side effect of 1% frequency within a range of ± 0.5% with
a power of 80%. For the immunogenic (seroconversion) component, 71 subjects are sufficient to evaluate a change in positivity from 71% to 90% (for example, for measles component) with 95% confidence and power of 80%. The corresponding figure for evaluating a positivity change from 25% to 75% (for example for mumps and rubella component) is only 18 children.

Results

The seroconversion data for the three components of the MMR vaccine is summarized in Table I. It is evident that the vaccine's immunogenicity was excellent; seroconversion to the various component was evident one week after vaccination and peaked at four weeks. The protective efficacy at four weeks as assessed by a positive IgG response ranged from 92% (mumps) to 100% (measles).

Surprisingly, despite a validated measles immunization at 9 months age, only 75% of children were 'protected' from this disease. The centre wise variation in this context was considerable; the seroconversion at Indore, Pune and Bombay centres being 50%, 82% and 93%, respectively. However, the second dose of measles in the form of MMR vaccine, resulted in seroconversion in all the subjects (Table I).

The reactogenicity data is summarized in Table II. Since no adverse effects were documented beyond six weeks this data has not been depicted in the table. The reactions, documented during the first three days were local pain and swelling, fever and/or cough in 96 out of 168 cases (57.1%). Usual reactions from the 4th to the 7th day were loose motions, transient rash, mild fever, cough and/or cold in 53 out of 168 cases (31.5%). Cold, cough, mild fever and painful parotitis were observed from 1 to 6 weeks in 19 out of 168 cases (11.3%). The pattern of these reactions was variable at each center. Local reactions were observed mostly at Pune (35/37 cases) in the first three days. Mild fever in the first three days was seen mostly at Pune (22/25 cases) and between fourth to the seventh day at Bombay (14/20 cases). This fever may possibly be related to local reactions and respiratory infections especially at the Pune center.

At the Pune center, two patients developed a painful parotitis, one on the 15th day and the other on the 20th day after immunization. These episodes were associated with mild fever which lasted for 2-3 days. Anaphylaxis, high fe-

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**TABLE I—Summary of Seroconversion Data**

<table>
<thead>
<tr>
<th>Component</th>
<th>Prevaccination</th>
<th>Time Period 1 week later</th>
<th>4 weeks later</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>67(75)</td>
<td>75(84)</td>
<td>89(100)</td>
</tr>
<tr>
<td>Mumps</td>
<td>11(12)</td>
<td>15(17)</td>
<td>82(92)</td>
</tr>
<tr>
<td>Rubella</td>
<td>12(13)</td>
<td>14(15)</td>
<td>88(99)</td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>20(22)</td>
<td>28(31)</td>
<td>40(45)</td>
</tr>
<tr>
<td>Mumps</td>
<td>26(29)</td>
<td>36(40)</td>
<td>55(62)</td>
</tr>
<tr>
<td>Rubella</td>
<td>5(6)</td>
<td>6(7)</td>
<td>27(30)</td>
</tr>
</tbody>
</table>

Figures without parentheses represent the number of children with positive immunoglobulin estimation, whereas the figures in parentheses are percentages.
ver, arthralgia or arthritic symptoms, paresthesia, encephalopathy, irritability and discomfort were not seen in any case.

**Discussion**

The indigenously produced MMR vaccine had an excellent immunogenicity to all the three components, which was comparable to the results of vaccines manufactured abroad(1-4,7). The vaccine also proved to be safe with a fairly low reactogenicity during the 6 months follow up. These findings are in the reported range for vaccines manufactured elsewhere. The commonest side effect was mild fever which is in concordance with earlier reports(3,17-21). Fortunately side effects like high fever, paresthesia(18), encephalopathy(19), irritability(20) and arthralgia(21) were not seen.

Surprisingly, only 75% of children were 'protected' from measles, despite a validated history of measles immunization at 9 months. This points to the need for consideration of a booster dose of measles immunization. Similar observations have been made by earlier workers(8-16). In the present series, MMR vaccine has acted as an effective booster in this context, and offered additional protection against mumps and rubella. Further studies are required to confirm these findings, before recommending MMR vaccine as a routine for children already immunized for measles.

It is concluded that the indigenously manufactured MMR vaccine has an excellent immunogenicity and low reactogenicity. MMR vaccination has a booster effect for measles seroconversion in children already immunized against this disease resulting in almost total seroconversion, thereby minimizing the 'vaccine failure cases'.

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**TABLE II—Summary of Documented Side Effects**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0-3 days</th>
<th>3-7 days</th>
<th>1-6 weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful parotitis</td>
<td>0</td>
<td>0</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Loose motions</td>
<td>0</td>
<td>3 (0.4)</td>
<td>0</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Transient rash</td>
<td>0</td>
<td>7 (0.8)</td>
<td>0</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Cold</td>
<td>8 (0.9)</td>
<td>14 (1.6)</td>
<td>6 (0.7)</td>
<td>28 (3.2)</td>
</tr>
<tr>
<td>Local pain and swelling</td>
<td>37 (4.3)</td>
<td>0</td>
<td>0</td>
<td>37 (4.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>26 (3.0)</td>
<td>9 (1.0)</td>
<td>5 (0.6)</td>
<td>40 (4.6)</td>
</tr>
<tr>
<td>Mild fever</td>
<td>25 (2.9)</td>
<td>20 (2.3)</td>
<td>6 (0.7)</td>
<td>51 (5.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>96 (11.1)</td>
<td>53 (6.1)</td>
<td>19 (2.2)</td>
<td>168 (19.4)</td>
</tr>
</tbody>
</table>

Figures in parenthesis represent percentages.
REFERENCES


19. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of sei-