Effectiveness of Biweekly Versus Daily Iron–Folic Acid Administration on Anaemia Status in Preschool Children

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Summary
Three-quarters of preschool children in India are anaemic. With the aim of identifying a cost-effective strategy for iron supplementation, the study objective was to assess the effectiveness of daily versus biweekly iron–folic acid (IFA: 20 mg elemental iron and 0.1 mg folic acid/tablet) on change in haemoglobin (Hb) levels of preschool children (3–6 years). This was a rural community-based effectiveness study in Uttar Pradesh, North India. IFA was given in two schedules: biweekly (2 tablets/dose) and daily (1 tablet/dose) for 1 year with fortnightly monitoring for adherence. A total of 400 and 403 children were enrolled in daily and biweekly regimes, respectively, of which 57.32 per cent and 50.25 per cent were anaemic (Hb < 11 g/dl) in each group. Adherence in biweekly and daily regimes was 89.05 per cent vs. 63.5 per cent. After 1 year, the mean Hb rise in daily and biweekly regime was 1.063 g/dl (SD: 1.6; p = 0.000) and 1.053 g/dl (SD: 1.73; p = 0.001), respectively. Reduction in point prevalence of anaemia was 65.7 per cent daily vs. 56.1 per cent in biweekly regimen (p = 0.0047). We conclude that biweekly as well as daily IFA administration is effective in raising Hb levels and decreasing community prevalence of anaemia significantly. However, since there is better adherence and lower drug costs associated with biweekly IFA administration, this can be considered for programme use.

Introduction
Of all the nutritional deficiencies, iron deficiency anaemia (IDA) is a major public health problem with nearly 70 million, i.e., about 60–70 per cent of all children below 6 years, suffering from it.1 According to the National Family Health Survey-2 in India, 74 per cent of children between 6 and 35 months are anaemic.2 IDA in infants and children can cause impaired motor development and co-ordination, impaired language development and scholastic performance, psychological and behavioural effects (inattention, fatigue, insecurity etc.), decreased physical activity,3–5 and decreased resistance to infection.6,7 Prevention of IDA in young children, therefore, is of high priority from a public health perspective. While iron–folic acid (IFA) supplementation is a simple and feasible strategy, there is currently insufficient data in India on the frequency of, as well as duration of, IFA administration.8 The current study was undertaken to assess the effectiveness of 1-tablet daily versus 2-tablets biweekly IFA, given to children aged 3–6 years, on the change in haemoglobin levels. IFA was delivered either through an existing government infrastructure (Integrated Child Health Development Services (ICDS)) or by the mother. A secondary objective was to assess the effectiveness of both systems.

Materials and Methods
Setting
This study was conducted in Nindura Block, Barabanki district, North India. Barabanki district has an area of 3825 km² and has 16 administrative blocks. Nindura block has 132 villages. Each village has about 75–150 houses and an average population of 1000. The block is further divided into 28 sub-centres, each with five to seven villages. For this study all sub-centres were listed alphabetically, serially numbered, and two were selected by random for assessment of the interventional strategies, one per sub-centre.

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Integrated Child Development Scheme (ICDS)

Under the ICDS services, there is an *anganwadi* centre (AWC) in each village with a population of about 1000. Each AWC has an *anganwadi* worker (AWW) who is responsible for running an informal school and a supplementary nutrition programme for preschool children. There are about 150 children aged 3–6 years per village, of which only about one-third are registered to obtain services of the AWC.

Interventions

The interventional drug was IFA. Each IFA tablet contained 20 mg elemental iron with 0.1 mg folic acid and was given in two schedules, either daily or biweekly for 1 year, and was intensively supervised. In the daily schedule, 1 tablet was given. In the biweekly schedule, 2 tablets of IFA were given twice a week on fixed days (Wednesday and Saturday).

Sub-centres of Shahpur Baxolia and Sipa Hidayatpur were included in this study. Children of Shahpur Baxolia were given IFA tablets biweekly for 1 year and those of Sipa Hidayatpur were given daily tablets for 1 year. The Department of Health, State Government and UNICEF sponsored IFA for the study. IFA was stored at the block level ICDS office from where the AWWs collected supplies for 2 months. IFA was given to the children either by the AWW, if they were registered and used the ICDS informal education services, or by the mother for non-registered children. On one particular day of every month the mothers of non-registered children came to the AWC to receive a monthly supply of IFA for their children.

Monitoring of intervention

A monitoring in-charge was responsible for each intervention type. He visited each AWC every 15 days to take an account of the drugs distributed to registered children. The monitoring in-charge also visited 20 randomly selected houses of non-registered children and collected information about the IFA tablet intake, including the number of pills consumed. Adherence was calculated by reported intake of IFA by the AWW for registered children and by counting the pills consumed by visiting homes of non-registered children. The proportion of children with 100 per cent adherence to each intervention regimen is reported.

Measurement of nutritional indices

A baseline survey of weight, height, and haemoglobin was done. Weight was measured using Uniscale 890 machines that could measure to the nearest 0.1 g. The weighing scale was checked by daily measuring of standard weights. Heights were measured by stadiometer. The staff were trained to use the instruments prior to fieldwork to minimize inter- and intra-observer variations. The accuracy of the machine was tested daily using the standard strip provided with the equipment. Ten per cent of the measurements were validated within 48 h. Hemocue (B-Haemoglobin photometer, Sweden) was used to estimate the haemoglobin levels, using the procedure described in the manual.

Participants

All children aged 3–6 years living in the villages were invited to participate with informed written parental consent. Excluded were children whose parents refused to give written informed consent or those who were likely to move within the next 3 months. Children identified as severely anaemic were given IFA in therapeutic doses under close supervision.

Baseline assessment was done for nutritional parameters. Thereafter assessment was done after 100 days and 1 year. Each subject was photographed, first at baseline for identification, and again at later assessments.

The primary outcome measure at the individual level was change in the haemoglobin level in 1 year. At the community level it was change in the prevalence of anaemic children (haemoglobin < 11 g/dl).

Sample size

Sample size was calculated to estimate 50 per cent (based on National Family Health Survey (NHFS) data) prevalence of anaemia with a required confidence interval of 5 per cent with an alpha level of 0.05 (two-tailed) and a power of 80 per cent, taking into consideration a design effect of 2. Four hundred children were required for this intervention type. The sample size was adequate to assess a 7.5 per cent change in the prevalence of anaemia with a power of 0.2 and a two-tailed alpha level of 0.05.

Statistical analysis

Data were entered in dBase and analysed using Epi2000 statistical software. Univariate analysis was done to describe the distribution of nutritional variables. Anaemia was defined as haemoglobin level < 11 g/dl. Univariate comparison of nutritional indices was done within each intervention type. Paired Student’s *t*-test was used to compare the change in haemoglobin within each intervention type. Across interventions, the change in haemoglobin was compared using unpaired *t*-test. The chi-squared test was used for categorical variables. A *p* value of < 0.05 was considered statistically significant.

To assess the feasibility of mothers and AWW giving IFA, we calculated the mean change in haemoglobin levels in registered and non-registered children in both the regimes. Paired Student’s *t*-test was used to compare changes in haemoglobin levels.
Results
A total of 803 children were recruited in the study; 403 children were recruited in the biweekly regime and 400 children in the daily regime. Mean age, weight, and height at recruitment was 3.96 years (SD: 0.86), 11.90 kg (SD: 2.11) and 85.98 cm (SD: 8.73), and was similar across both interventions (data not shown). Male:female ratio was 6:5. Loss to follow-up at 100 days and 1 year was 8.59 per cent and 8.34 per cent, respectively (Table 1). Adherence to interventions at 100 days and 1 year is shown in Table 2. Mean change in haemoglobin level overall and among registered and non-registered children at 100 days and 1 year are given in Table 3. Change in prevalence of anaemia after 100 days and 1 year of intervention is given in Table 4. Reduction in point prevalence of anaemia was 65.7 per cent in the daily regime vs. 56.1 per cent in the biweekly regime ($p = 0.005$).

Discussion
Baseline prevalence of anaemia in children aged 3–6 years was 53.79 per cent. Daily as well as biweekly IFA administration, delivered through the existing governmental systems and with intensive monitoring, resulted in a rise in the mean haemoglobin levels of individuals and a reduction in community prevalence of anaemia. A multi-centre study done by the Food and Nutrition Board and UNICEF reported that 60 per cent of children (1–5 years) in Uttar Pradesh were anaemic, which was similar to the prevalence of anaemia found by us. Studies done in other parts of India have reported a prevalence of anaemia in children between 38.9 and 86.2 per cent. Supplementation of iron is a simple strategy to reduce the prevalence of anaemia. The preventive dose of iron recommended for children aged 2–5 years is 2 mg/kg of body weight in a daily regime and 3 mg/kg body weight in a biweekly regime. UNICEF and WHO recommend the use of iron supplements, such as ferrous sulphate and iron polymaltose complex, for the prevention and treatment of iron-deficiency anaemia in infants and children. Non-heme iron, in the form of ferrous sulphate, has been used in most supplementation programmes because of its low cost, better shelf-life and fewer side-effects.

### Table 1
Loss to follow-up at 100 days and 1 year

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Number of children enrolled</th>
<th>After 100 days of IFA intake</th>
<th>After 1 year of IFA intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biweekly</td>
<td>403</td>
<td>25 (6.20)</td>
<td>33 (8.1)</td>
</tr>
<tr>
<td>Daily</td>
<td>400</td>
<td>44 (11.00)</td>
<td>34 (8.5)</td>
</tr>
<tr>
<td>Total</td>
<td>803</td>
<td>69 (8.59)</td>
<td>67 (8.34)</td>
</tr>
</tbody>
</table>

### Table 2
Percent adherence to IFA amongst registered, non-registered children and in both groups

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Registered $n$ (%)</th>
<th>Non-registered $n$ (%)</th>
<th>Both $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biweekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 100 days</td>
<td>113 (90.01)</td>
<td>196 (87.99)</td>
<td>309 (89.05)</td>
</tr>
<tr>
<td>at 1 year</td>
<td>132 (93.23)</td>
<td>266 (85.43)</td>
<td>398 (88.02)</td>
</tr>
<tr>
<td>Daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 100 days</td>
<td>82 (58.70)</td>
<td>154 (66.84)</td>
<td>236 (63.51)</td>
</tr>
<tr>
<td>at 1 year</td>
<td>101 (66.78)</td>
<td>134 (61.05)</td>
<td>235 (63.51)</td>
</tr>
</tbody>
</table>

### Table 3
Mean haemoglobin level and mean change in haemoglobin at the time of enrolment, at 100 days and 1 year in registered as well as non-registered children of biweekly and daily regime

<table>
<thead>
<tr>
<th></th>
<th>Biweekly</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At enrolment</td>
<td>At 100 days</td>
</tr>
<tr>
<td>Both registered and non-registered children</td>
<td>Mean Hb</td>
<td>9.78 ± 1.5</td>
</tr>
<tr>
<td>Mean change in Hb ± SD</td>
<td>0.296 ± 1.65</td>
<td>1.053 ± 1.73</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>Registered children</td>
<td>Mean change in Hb ± SD</td>
<td>0.360 ± 1.69</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Non-registered children</td>
<td>Mean change in Hb ± SD</td>
<td>0.153 ± 1.56</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.292</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Various workers have reported a decline in the prevalence of anaemia after IFA administration in children\textsuperscript{15,16} and adolescent girls.\textsuperscript{17} In the present study both biweekly and daily IFA resulted in a rise in haemoglobin levels and a reduction in the community prevalence of anaemia. A study on Nepalese adolescent girls revealed that weekly supplementation given under supervision was as effective as daily supplementation.\textsuperscript{18} In a meta-analysis it was concluded that weekly iron supplementation is likely to be less effective than daily administration, except in situations where supervision is possible with a weekly regime but not with a daily regime.\textsuperscript{19} It has also been argued that poor adherence to intermittent IFA supplementation is to be expected, similar to that seen for malaria prophylaxis.\textsuperscript{20}

National consultation for control of nutritional anaemia reports that administration of a daily dose of iron may result in saturation of intestinal mucosa with iron, and thus can block further absorption.\textsuperscript{1} Since the intestinal mucosa turns over once in every 5–6 days, intermittent iron supplementation is expected to be much better absorbed.\textsuperscript{1} Viteri, \textit{et al.}\ found that absorption from a single dose of iron reduces from 30–40 per cent on the first day to as low as 3–6 per cent after a few days of continuous daily administration.\textsuperscript{21} Other studies have reported that continued daily administration could lead to ‘tiredness’ of intestinal mucosa.\textsuperscript{21,22} It has been reported that weekly supplements reduce side-effects\textsuperscript{23,24} and lower the cost, may improve compliance and reduce oxidative stress,\textsuperscript{25} and maintain iron stores for a longer period when iron is stopped.\textsuperscript{23}

It has also been reported in some studies that the expected degree of improvement in iron status depends on the total amount of iron consumed during the period.\textsuperscript{11} Since total iron consumption is greater in a daily regime, a corresponding greater mean rise in haemoglobin level was found among them (Table 3). A major obstacle to iron supplementation, in both developing and developed countries, has been poor adherence to treatment.\textsuperscript{26} In the present study, with same intensity of supervision, adherence was greater in biweekly (88.02 per cent) than in daily regimes (63.51 per cent). There are individual factors\textsuperscript{1} and community characteristics\textsuperscript{9} which effect adherence.

AWWs adhered more to IFA than the mothers, possibly because they were directly trained for IFA administration by the project staff. However, unsupervised motivation of the mothers was done by the AWW. Sustained motivation to administer tablets was due to intensive monitoring and supervision for the entire duration. IEC has been found to be effective in improving adherence.\textsuperscript{8}

This was a community-based effectiveness study. The loss to follow-up in assessment of outcome was very small. Intensive supervision through external monitors was done in both the arms. Intervention was delivered through an existing healthcare system and IFA from a usual government supply was used. Thus the work can be replicated, scaled and sustained. We demonstrated that the intervention can be given either by the mothers or the AWWs.

Iron deficiency anaemia in preschool children can be effectively prevented and controlled by IFA administration through a community-based approach. Biweekly IFA administration has better adherence with supervision and is therefore the dominant strategy. In India there is a need to develop an effective national policy for anaemia control in preschool children.

### References


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**Table 4: Impact of iron supplementation on prevalence of anaemia**

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Duration</th>
<th>Anaemic children (Hb &lt; 11 g/dl) n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biweekly</td>
<td>Presupplementation (n = 403)</td>
<td>231 (57.32)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Post-supplementation (n = 369)</td>
<td>92 (25.14)</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>Presupplementation (n = 400)</td>
<td>201 (50.25)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Post-supplementation (n = 361)</td>
<td>58 (17.22)</td>
<td></td>
</tr>
</tbody>
</table>
14. Beaton GH, McCabe GP. Efficacy of intermittent iron supplementation in the control of iron deficiency anaemia in developing countries. The Micronutrient Initiative, Canada, 1999