Iron and folic acid supplements in pregnancy improve child survival in Indonesia\textsuperscript{1–3}

Michael J Dibley, Christiana R Titaley, Catherine d’Este, and Kingsley Agho

**ABSTRACT**

**Background:** Several trials have shown that iron-folic acid supplements during pregnancy protect newborns against preterm delivery and early neonatal death, but the impact beyond the neonatal period is unclear.

**Objective:** We determined whether live-born children $<5$ y of age born to mothers who used antenatal iron-folic acid supplements had reduced risk of death.

**Design:** Pooled 1994, 1997, 2002–2003, and 2007 Indonesia Demographic and Health Survey data were used to examine the relation between the use of iron-folic acid supplements and child death in 3 cumulative (0–30 d, 0–11 mo, and 0–4 y) and 4 mutually exclusive (first day of life and 1–30 d, 1–11 mo, and 1–4 y of age) time periods. Risk of death was estimated by using Cox regression to control for 19 potential confounders.

**Results:** Survival information for 52,917 singleton live-born infants and 1525 deaths of children $<5$ y of age was examined. After adjustment for potential confounders, risk of death of children $<5$ y of age was reduced significantly by 34\% if the mother consumed any iron-folic acid supplements [adjusted HR (aHR): 0.66; 95\% CI: 0.53, 0.81; $P < 0.001$]. This protective effect was greatest for deaths on the first day of life (aHR: 0.40; 95\% CI: 0.21, 0.77; $P = 0.005$) but was also shown for neonatal deaths on days 1–30 of life (aHR: 0.69; 95\% CI: 0.49, 0.97; $P = 0.035$) and postneonatal deaths (aHR: 0.74; 95\% CI: 0.56, 0.99; $P = 0.044$). There was a strong dose response of greater protection from death of children $<5$ y of age with increasing numbers of iron-folic acid supplements consumed.

**Conclusion:** In developing countries increased use of antenatal iron-folic acid supplements will reduce deaths of children $<5$ y of age, especially in the first year of life. *Am J Clin Nutr* 2012;95:220–30.

**INTRODUCTION**

Globally, $\sim$7.7 million children $<5$ y of age died in 2010, and of these deaths, 3.1 million children died in the neonatal period (0–27 d), 2.3 million children died by 11 mo, and 2.3 million children died at 1–4 y of age (1). These numbers represent a 35\% decline in deaths of children $<5$ y of age in developing countries from 11.9 million deaths in 1990, which is an average annual decline of 2.1\% (1). However, additional substantial progress is needed to reach the average annual decline of 4.4\% required to achieve the Millennium Development Goal for child survival by 2015.

Although average global declines in neonatal (2.1\%), postneonatal (2.3\%), and child (2.2\%) mortality from 1990 to 2010 were similar, this was not the case in low- and middle-income countries where the decline in neonatal mortality has been slower than for postneonatal and child mortality (1). For example, in Southeast Asia, the annual rate of decline in child mortality is $\sim$3 times greater than for neonatal mortality (1).

Similar trends have been reported in Indonesia where IDHSs\textsuperscript{4} show that postneonatal mortality decreased by 50\% and child mortality by 55\% between 1991 and 2007, but neonatal mortality only decreased by 40\% (2, 3). Achievement of the child-survival Millennium Development Goal target will require more effective interventions especially for neonatal deaths.

Observational studies showed that low hemoglobin in early pregnancy is associated with an increased risk of low birth weight, preterm birth (but not small-for-gestational age) (4), and perinatal mortality (5). Over a number of years, studies showed that IFA supplementation in pregnancy is associated with reduced risk of low birth weight and preterm delivery (6–8), and recent trials have confirmed these findings in healthy, iron-sufficient women (9–12). In developing countries, preterm delivery is one of the main contributors to neonatal deaths (13, 14), although its role in postneonatal mortality is not known.

In a recent trial from China, there was a 54\% reduction in early neonatal mortality in women who received IFA supplements compared with folic acid alone (9) and an increase in the duration of gestation with a significant reduction in risk of early preterm delivery. In Nepal, there was a significant 31\% reduction in mortality of children aged 0–7 y whose mothers received IFA supplements than in control subjects (15). This trial provided the first evidence that the beneficial effects of pregnancy IFA supplementation may extend beyond the neonatal period.

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\textsuperscript{4}Abbreviations used: aHR, adjusted HR; CB, census block; IDHS, Indonesia Demographic and Health Survey; IFA, iron and folic acid; PAR, population attributable risk.

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In Indonesia, IFA supplementation for pregnant women has been a consistent national health policy and program since the early 1990s. The Ministry of Health recommends that pregnant women in the second trimester take 60 mg iron and 0.25 mg folic acid daily for 90 d. Women obtain their IFA supplements from a variety of sources, including health care facilities, mainly from midwives when attending antenatal care checkups, through self-purchase over the counter from drug shops, or through trained traditional birth attendants (16).

Our earlier analyses of the 1994, 1997, and 2002–2003 IDHSs showed a protective effect of antenatal IFA supplementation on early neonatal mortality (17). The aim of the current study was to examine how long this protective effect extended into childhood; ie, we tested whether live-born infants of mothers who reported IFA supplementation during pregnancy had improved survival during their first 5 y of life.

METHODS

Data sources

Demographic and Health Surveys are nationally-representative household surveys that collect data on a wide range of population, health, and nutrition indicators (18) and have been conducted in Indonesia approximately every 4 y since 1987 (3). Demographic and health information is collected by interview from ever-married women aged 15–49 y and, since 2002–2003, ever-married men aged 15–54 y and recorded in the following 3 questionnaires: the Household Questionnaire, Women’s Questionnaire, and Men’s Questionnaire. All information collected is self-reported by the women and men interviewed.

In interviews of ever-married women of reproductive age, a complete history of their births was recorded, and for the last birth during the 5 y before being interviewed, additional details about the antenatal, delivery, and postnatal care services the women received were recorded. The birth history listed all of the woman’s live births in chronologic order, the date of the birth of each child, the singleton or multiple status of the birth, the sex of the child, the survival status of the child on the day of the interview, and if deceased, the date of death.

These surveys use a multistage, stratified, cluster random-sampling method, which has been described in detail (18). As an example, the sample for the 2007 IDHS was designed to provide estimates for the country as a whole, each province, and urban and rural areas (3). The primary sampling unit was CBs. The sample was stratified by urban and rural areas in each province, and rural areas (3). The primary sampling unit was CBs.

The data for this study were from the 1994, 1997, 2002–2003, and 2007 IDHSs (3, 19–21). In this pooled dataset, information was available from 119,356 ever-married women of reproductive age, which consisted of 28,168 women from the 1994 survey, 28,810 women from the 1997 survey, 29,483 women from the 2002–2003 survey, and 32,895 women from the 2007 survey. The analyses used survival information from 52,917 singleton live-born infants of the most recent birth of the mother in ≤5 y before her interview. Only the woman’s most recent birth was used in the analyses because only those births had detailed information about the use of perinatal health services and to limit the potential for differential recall of events from mothers who had delivered at very different durations before the interview. Women who had not had a delivery in the past 5 y before the survey were excluded from this analysis. Participation in the IDHS has always been high with an average individual response rate >97.5% for the surveys examined (3, 19–21).

Outcomes and study factors

The primary outcomes of this study were child mortality in 3 progressively longer cumulative time periods and in 4 mutually exclusive time periods. The mortality outcomes examined in different cumulative time periods included neonatal mortality (deaths after birth through 30 d of age), infant mortality (deaths after birth through 11 mo of age), and mortality of children <5 y of age (deaths after birth through 4 y of age) (22). The mortality outcomes examined in each of the mutually exclusive time periods included day 1 mortality (deaths after birth on the first day of life), 1–30-d mortality (deaths after the first day of life through 30 d of age), 1–11-mo mortality (deaths from 1–11 mo of age), and 1–4-y mortality (deaths from 1–4 y of age).

The main exposure variable examined was the maternally reported use of any IFA supplements during the most recent pregnancy in the 5 y before the interview. The questions used in the IDHS related to the use of IFA supplements were as follows: “During this pregnancy, were you given or did you buy any iron tablets,” and “For how many days during this pregnancy did you take the iron tablets?” Furthermore, combinations of use of any antenatal care services and any use of IFA were also examined to isolate the effects of the use of IFA supplements independent of the use of other antenatal care services. The question for the use of antenatal care services in the IDHS was “Did you see someone for antenatal care for this pregnancy?”

A potential dose response was assessed by comparing the effects on mortality outcomes when women reported taking no, 1–29, 30–89, 90–119, or ≥120 supplements. Reports of consumption of >240 supplements during pregnancy were considered implausible (either mistaken recall or data recording errors) and were excluded from these dose-response analyses. The effect of starting supplements progressively later in pregnancy (first, second, or third trimester) was also examined by using the date of the first antenatal health care examination as a surrogate for the start of IFA supplementation.

Potential confounding factors were examined on the basis of the Mosley and Chen framework of factors that influence child survival in developing countries (23), which was adapted for the data available in the IDHS. In total, 19 potential confounders were examined and organized into 2 main groups as follows: community-level and socioeconomic status characteristics and proximate determinants that consisted of maternal and neonatal characteristics and perinatal health care services. There were 6 community-level and socioeconomic status variables assessed in the analysis, which included the urban or rural areas of geographic regions that cover groups of provinces (Java-Bali, Sumatera, and Eastern Indonesia), the average cluster coverage of Bacillus Calmette-Guérin vaccine against tuberculosis vaccination or average cluster coverage of
measles vaccination, maternal level of attained education, mater-
nal marital status, parental occupation, and household wealth
index. In proximate determinants, there were 7 maternal and
neonatal characteristics assessed, which included maternal age
at childbirth, child sex, a combination of birth rank and birth
interval, the mother’s desire for the pregnancy, any reported
delivery complications (including prolonged labor, excessive
vaginal bleeding, fever or foul smelling, or convulsions), com-
bined reported birth size and duration of pregnancy (born early
or on time), and if ever breastfed. Also examined in the prox-
imate determinants were 4 perinatal health care variables (ie,
tenatal care, type of birth attendant, mode of delivery, and
place of delivery). Also adjusted were the duration of the recall
period at interview and the year of the child’s birth.

A household wealth index variable was constructed as an
indicator of household economic status by using the pooled IDHS
data and a principal component analysis (24) of 11 household
facilities and assets (ie, source of drinking water, type of toilet,
main material of floor, main material of wall, availability of
electricity, possession of radio, television, or fridge, and bicycle,
motorcycle, or car ownership). This household wealth index was
used to rank households across the 4 surveys and was divided into
quintiles for analysis.

In the analysis, the subjective assessment by mother of the size
at birth of her infant (smaller than average, average, and larger
than average sized) was used as a proxy for birth weight because
approximately one-third of infants were not weighed at birth.
Previously, we demonstrated a close correspondence between
mean birth weight and this self-reported estimate of the size of the
newborn (17).

The birth-size variable was combined with the reported timing
in pregnancy of the delivery, (ie, if the infant was born early or
born at the expected time). The way this information was col-
lected varied slightly across the surveys. For the 1994 and 1997
IDHSs it was based on the mother’s report of whether or not the
infant was born on time or born prematurely (19, 20), whereas for
the 2002 and 2003 and 2007 IDHSs, it was based on the mother’s
report of whether or not the labor occurred before the ninth month
of pregnancy (3, 21).

The variables of birth rank and birth interval were combined as
a 5-category composite variable that consisted of first birth-rank
infants, second and third birth-rank infants with a previous birth
interval >2 y, second and third birth-rank infants with a pre-
vious birth interval ≤2 y, fourth birth-rank infants with a pre-
vious birth interval >2 y, and fourth birth-rank infants with a
previous birth interval <2 y.

To adjust for variations in the recall period, a variable was
constructed as the difference in days between the date of the birth
of the child and the date of interview. To adjust for secular trends
in maternal iron status and development of perinatal health
services, a variable with the year of birth of the child was
constructed. Both of these variables were retained in all re-
gression models.

Statistical analysis

Characteristics of the study population and factors that were
potentially associated with the mortality outcomes were examined
with frequency tabulations. Cox proportional hazards regression was
used to examine associations between study factors and mortality
outcomes, initially with bivariate regression analysis for each factor
but followed by multivariate analyses to assess the independent
effects after other covariates were controlled for.

A staged modeling strategy was used. In the first step, all
community and socioeconomic variables were used to construct
a model by backward elimination to remove the nonsignificant
factors by using a significance level of 0.05. Two variables were
selected a priori to be retained in all models (ie, the duration of
the maternal recall period and the year of birth). In the second step,
the pregnancy and delivery health care service variables, use of
antenatal care in the pregnancy, institutional compared with home
delivery, and trained compared with untrained delivery attendants
were assessed in the model with the community and socioeco-
omic variables that were associated with mortality outcomes. In
all models, the type of delivery attendance was retained a priori
because of its claimed protective effects especially for neonatal
survival (25). In the final stage, variables that reflected the use of
IFA supplementation during pregnancy (ie, any reported use of
IFA, the number of IFA supplements used, and stage of pregnancy
when supplementation started) were assessed individually in the
model with the significant community, socioeconomic, preg-
nancy, and delivery health care service variables. Throughout the
modeling process, variables were retained by using a level of
significance of 0.05 unless they had been a priori selected for
inclusion.

The effects of the study factors were assessed with HRs and their
95% CIs derived from the adjusted Cox proportional hazards
models. Stata/MP software (version 10.00, 2007; StataCorp) was
used for all analyses, and the models were fitted by using the
survey commands to adjust for the cluster-sampling survey design.

Plots of cumulative mortality for neonatal deaths and deaths of
children <5 y of age by the use of IFA supplementation during
pregnancy were constructed from the adjusted Cox propor-
tional hazards models for mortality at <5 y of age with the use of
curve and cunnhaz commands in the Stata/MP software (version
10.00, 2007; StataCorp). The results of models that show the
effects on deaths of children <5 y of age of different combina-
ations of the use of antenatal care and IFA supplements in preg-
nancy and different total number of supplements and the timing of
start of supplementation were presented by using forest plots. The
Cochran-Armitage test for trend (26) was used to assess for the
presence of a trend between mothers who reported the use of
antenatal care in the pregnancy, institutional compared with home
delivery, and trained compared with untrained delivery attendants
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Cochran-Armitage test for trend (26) was used to assess for the
presence of a trend between mothers who reported the use of
different total number of supplements and the timing of the start
of supplementation on deaths of children <5 y of age.

PAR was calculated to establish total risk of mortality outcomes
of children <5 y of age in the general population that was at-
tributable to women who did not take IFA supplements during
pregnancy or who did not take >90 supplements starting in the
first trimester. These calculations assumed that the association
between IFA supplementation and mortality was causal and that
removal of IFA supplementation had no effect on the distribu-
tion of other risk factors for mortality. We used the following
formula for these estimations (27–29):

\[ \text{PAR} = \frac{\text{aHR} - 1}{\text{aHR}} \]

where aHR was the adjusted hazard ratio for deaths of children
<5 y of age who were born to women who did not take IFA
Iron in pregnancy reduces deaths of <5-y-olds

RESULTS

In the 52,917 singleton live-born infants from the most recent delivery in ≤5 y before interview date, there were 1525 deaths of children <5 y of age of which 206 deaths were neonatal deaths on the first day of life, 496 deaths were neonatal deaths from days 1–30 of life, 616 deaths were postneonatal deaths from 1 to 11 mo of age, and 207 deaths were young-child deaths from 1–4 y of age. The percentage of neonatal deaths out of all deaths of children <5 y of age was 45% in 1994, 44% in 1997, 51% in 2002–2003, and 47% in 2007.

The distribution and trends in the use of pregnancy, delivery, and child health care services provided to mothers of singleton infants is shown in Table 1. Approximately 90% of infants were born to mothers who received antenatal care services, and 71% of mothers reported the use of IFA supplements in pregnancy, with 21% of mothers who took 1–29 supplements and 26% of mothers who took 30–89 supplements, but only 8% of mothers took 90–119 supplements, and 11% of mothers took ≥120 supplements. There were 1454 mothers (2.8%) who reported taking >240 capsules, and these observations were excluded from analyses that examined the effects of the number of supplements on mortality outcomes. The percentage of women who consumed ≥90 IFA supplements increased from 13% in the 1994 IDHS to 21% in the 2007 IDHS. More than one-half of women started antenatal care and the use of IFA supplements in the first trimester of pregnancy, and this percentage steadily increased from 45% in the 1994 IDHS to 58% in the 2007 IDHS.

Approximately one-third of women delivered in a health facility, but this percentage progressively increased from 18% in the 1994 IDHS to 48% in 2007 IDHS. Nearly 60% of women reported delivery assistance with a trained attendant and coverage of trained birth attendants nearly doubled from 41% in the 1994 IDHS to 74% in the 2007 IDHS (Table 1). The average coverage of Bacillus Calmette-Guérin vaccine against tuberculosis vaccination in the survey clusters was high and only increased slightly from 76% in the 1994 IDHS to 81% in the 2007 IDHS. The average coverage of measles vaccination was lower (63%) but it also increased from 57% in the 1994 IDHS to 66% in the 2007 IDHS.

Results of a multivariate analysis of community and socioeconomic factors and proximate determinants, including perinatal health services, and their relation with mortality of children <5 y of age are shown in Table 2. There was regional variation in risk of death of children <5 y of age with higher mortality of children <5 y of age in rural Eastern Indonesia than in urban Java and Bali. As expected, higher levels of maternal education protected against deaths of children <5 y of age; eg, children of mothers with completed secondary education or higher had 47% reduced risk of death at <5 y of age than did children of mothers with no education (aHR: 0.53; 95% CI: 0.36–0.77; P = 0.001). Risk of deaths of children <5 y of age was higher if both parents worked or if the father was unemployed and if the mother was not currently married. Male infants and infants of higher parity and with shorter birth intervals also had increased risks of deaths at <5 y of age. There were substantially increased risks of deaths of children <5 y of age whose mothers reported they were born early and of average size (aHR: 3.78; 95% CI: 2.11, 6.79; P < 0.001) or born early but of smaller than average size (aHR: 9.22; 95% CI: 6.52, 13.03; P < 0.001). Of the perinatal health care services examined (ie, mode of delivery, place of delivery, delivery attendance, and use of antenatal care), only delivery attendance and antenatal care demonstrated a significant protective effect on mortality of children <5 y of age after adjustment for all significant community and socioeconomic status characteristics (Table 2).

Results of multivariate models of effects of the use of any IFA supplementation on cumulative child-mortality indicators and child mortality over mutually exclusive time periods are shown in Table 3. Any reported use of IFA supplementation during pregnancy significantly reduced risk of child deaths for all 3 cumulative mortality indicators to a similar extent after adjustment for potentially confounding community, socioeconomic, and proximate child-mortality determinants, including other perinatal health services. There was no consistent pattern across surveys in the magnitude of the protective effect of IFA supplementation on cumulative child-mortality indicators. For example, there was a 28% reduction (aHR: 0.72; 95% CI: 0.51; 1.02) in the mortality of children <5 y of age in the 1994 survey, a 39% reduction (aHR: 0.61; 95% CI: 0.44, 0.85) in the mortality of children <5 y of age in the 1997 survey, a 29% reduction (aHR: 0.71; 95% CI: 0.42, 1.22) in the mortality of children <5 y of age in 2002–2003 survey, and a 26% reduction (aHR: 0.74; 95% CI: 0.47, 1.18) in the mortality of children <5 y of age in the 2007 survey. Also, as shown in Table 3, unadjusted HRs and aHRs for the use of IFA supplementation for these mortality indicators differed substantially, which indicated that important confounding factors had been controlled for in the analysis.

The use of IFA supplementation during pregnancy was also protective for child deaths in each of the mutually exclusive time periods examined except for the young-child period (1–4 y of age). The greatest protection was for the first day of life when risk of death was significantly reduced by 60% (aHR: 0.40; 95% CI: 0.21, 0.77; P = 0.005) for infants whose mother reported the use of IFA supplementation in pregnancy. This protective effect was shown throughout the remaining neonatal period (days 1–30 of life) during which risk of death was significantly reduced with the use of IFA supplementation in pregnancy by 31% (aHR: 0.69; 95% CI: 0.49, 0.97; P = 0.035). This protective effect also extended into the postneonatal period (1–11 mo of age) during which risk of death was significantly reduced with the use of IFA supplementation in pregnancy by 31% (aHR: 0.69; 95% CI: 0.49, 0.97; P = 0.035). In the young-child period (1–4 y of age), the use of IFA supplementation was protective for risk of child deaths, but this effect was not significant.

Plots of adjusted cumulative mortality for deaths of children <5 y of age by use of IFA supplementation during pregnancy are shown in Figure 1. These plots were constructed by using the model for mortality of children <5 y of age (0–4 y of age) reported in Table 3. In the first plot (Figure 1A), the cumulative mortality during the neonatal period was lower in infants whose mothers used IFA supplementation during pregnancy. This difference in cumulative mortality was evident from immediately...
after birth, and steadily increased. In the second plot (Figure 1B), the lower cumulative mortality for infants whose mothers used IFA supplementation during pregnancy was seen to continue during the postneonatal period and through to the end of the fourth year after birth.

Forest plots of effects of antenatal care and IFA supplementation, the number of IFA supplements, and the timing of the start of IFA supplementation during pregnancy on mortality of children <5 y of age in Indonesia between 1994 and 2007 are shown in Figure 2. In Figure 2A, the effects of different combinations of the use of IFA supplements and antenatal care on risk of death of children <5 y of age are illustrated. Compared with women who did not receive antenatal care services or IFA supplements, risk of mortality of children <5 y of age reduced significantly in children whose mothers reported the use of IFA supplements alone but no antenatal care (aHR: 0.48; 95% CI: 0.23, 0.98; \( P = 0.048 \)) and in children whose mothers reported the use of both IFA supplements and antenatal care (aHR: 0.55; 95% CI: 0.42, 0.73; \( P = 0.001 \)), but only a borderline significant reduction was shown in children of mothers who attended antenatal care services but did not use IFA supplements (aHR: 0.72; 95% CI: 0.52, 0.99; \( P = 0.048 \)).

The effects of different total numbers of IFA supplements consumed during pregnancy on risk of death of children <5 y of age are illustrated in Figure 2B. Compared with women who did not receive antenatal care services or IFA supplements, risk of mortality of children <5 y of age reduced significantly in children whose mothers reported the use of 1–29 IFA supplements (aHR: 0.64; 95% CI: 0.48, 0.84; \( P = 0.002 \)) and in children whose mothers reported the use of 90–119 IFA supplements (aHR: 0.58; 95% CI: 0.44, 0.76; \( P = 0.001 \)), but only a borderline significant reduction was shown in children of mothers who reported consumption of 120 or more IFA supplements (aHR: 0.74; 95% CI: 0.55, 0.99; \( P = 0.048 \)).
Perinatal health services
Proximate determinants
Community and socioeconomic variables

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<td>0.94</td>
<td>0.72, 1.24</td>
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<tr>
<td>Primary completed</td>
<td>16,809</td>
<td>31.8</td>
<td>0.54</td>
<td>0.42, 0.70</td>
<td>&lt;0.001</td>
<td>0.96</td>
<td>0.73, 1.27</td>
<td>0.771</td>
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</tr>
<tr>
<td>Secondary not completed</td>
<td>9957</td>
<td>18.8</td>
<td>0.41</td>
<td>0.31, 0.53</td>
<td>&lt;0.001</td>
<td>0.87</td>
<td>0.63, 1.21</td>
<td>0.411</td>
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<tr>
<td>Secondary completed and tertiary</td>
<td>11,743</td>
<td>22.2</td>
<td>0.23</td>
<td>0.17, 0.32</td>
<td>&lt;0.001</td>
<td>0.53</td>
<td>0.36, 0.77</td>
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<tr>
<td>Maternal marital status</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Currently married</td>
<td>51,538</td>
<td>97.4</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
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<tr>
<td>Formerly married (divorced, separated, or widowed)</td>
<td>1379</td>
<td>2.6</td>
<td>1.89</td>
<td>1.26, 2.84</td>
<td>0.002</td>
<td>1.63</td>
<td>1.09, 2.42</td>
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<tr>
<td>Parental occupation</td>
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</tr>
<tr>
<td>Nonworking mother and working father</td>
<td>28,857</td>
<td>54.5</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Working mother and working father</td>
<td>22,925</td>
<td>43.3</td>
<td>1.28</td>
<td>1.08, 1.53</td>
<td>0.006</td>
<td>1.32</td>
<td>1.10, 1.57</td>
<td>0.002</td>
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<tr>
<td>Unemployed father</td>
<td>999</td>
<td>1.9</td>
<td>2.01</td>
<td>1.0, 3.82</td>
<td>0.034</td>
<td>1.95</td>
<td>1.06, 3.61</td>
<td>0.032</td>
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<tr>
<td>Working mother and nonworking father</td>
<td>28,857</td>
<td>54.5</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Working father and nonworking mother</td>
<td>22,925</td>
<td>43.3</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
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</tr>
<tr>
<td>Working father and working mother</td>
<td>22,925</td>
<td>43.3</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
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<tr>
<td>Nonworking mother and nonworking father</td>
<td>28,857</td>
<td>54.5</td>
<td>1.00</td>
<td>Reference</td>
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<tr>
<td>Proximate determinants</td>
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<tr>
<td>Sex of child</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>25,568</td>
<td>48.3</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
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</tr>
<tr>
<td>M</td>
<td>27,348</td>
<td>51.7</td>
<td>1.28</td>
<td>1.08, 1.53</td>
<td>0.006</td>
<td>1.32</td>
<td>1.10, 1.57</td>
<td>0.002</td>
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<tr>
<td>Birth rank and interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second or third child, interval &lt;2 y</td>
<td>19,816</td>
<td>37.5</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td></td>
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<tr>
<td>First child</td>
<td>17,053</td>
<td>32.2</td>
<td>0.94</td>
<td>0.75, 1.18</td>
<td>0.592</td>
<td>0.90</td>
<td>0.71, 1.14</td>
<td>0.385</td>
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<tr>
<td>Second or third child, interval ≥2 y</td>
<td>3351</td>
<td>6.3</td>
<td>1.92</td>
<td>1.37, 2.70</td>
<td>&lt;0.001</td>
<td>1.72</td>
<td>1.23, 2.42</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Fourth or higher child, interval ≥2 y</td>
<td>10,775</td>
<td>20.4</td>
<td>1.83</td>
<td>1.49, 2.26</td>
<td>&lt;0.001</td>
<td>1.36</td>
<td>1.09, 1.69</td>
<td>0.006</td>
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</tr>
<tr>
<td>Larger than average</td>
<td>26,507</td>
<td>50.1</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Average size and born on time</td>
<td>435</td>
<td>0.8</td>
<td>3.22</td>
<td>1.78, 5.83</td>
<td>&lt;0.001</td>
<td>3.78</td>
<td>2.11, 6.79</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smaller than average and born on time</td>
<td>6586</td>
<td>12.4</td>
<td>1.92</td>
<td>1.55, 2.37</td>
<td>&lt;0.001</td>
<td>1.81</td>
<td>1.46, 2.24</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Smaller than average and born early</td>
<td>486</td>
<td>0.9</td>
<td>9.42</td>
<td>6.64, 13.37</td>
<td>&lt;0.001</td>
<td>9.22</td>
<td>6.52, 13.03</td>
<td>&lt;0.001</td>
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<tr>
<td>Larger than average</td>
<td>17,475</td>
<td>33.0</td>
<td>0.96</td>
<td>0.78, 1.17</td>
<td>0.665</td>
<td>0.96</td>
<td>0.78, 1.18</td>
<td>0.682</td>
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<tr>
<td>Perinatal health services</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth attendance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TBA, other untrained, or none</td>
<td>22,129</td>
<td>41.8</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Health professional</td>
<td>30,754</td>
<td>58.1</td>
<td>0.47</td>
<td>0.39, 0.55</td>
<td>&lt;0.001</td>
<td>0.81</td>
<td>0.66, 1.00</td>
<td>0.047</td>
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</tr>
<tr>
<td>ANC service by health workers</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ANC</td>
<td>5116</td>
<td>9.7</td>
<td>1.00</td>
<td>Reference</td>
<td>—</td>
<td>1.00</td>
<td>Reference</td>
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<td></td>
</tr>
<tr>
<td>ANC by health workers</td>
<td>47,480</td>
<td>89.3</td>
<td>0.35</td>
<td>0.29, 0.43</td>
<td>&lt;0.001</td>
<td>0.62</td>
<td>0.48, 0.80</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

¹ aHR, adjusted HR; ANC, antenatal care; TBA, traditional birth attendant.
² Data on 3850 cases were missing and were excluded from the analysis.
³ Results of the Cox proportional hazards regression analysis. Weighting was applied to adjust for the multi-stage sampling design.
⁴ Adjusted for recall period, year of birth of the child, average cluster coverage of measles vaccination, and ever-breastfed status.

The effects of variations in the timing of the start of IFA supplementation during pregnancy on risk of death of children <5 y of age are illustrated in Figure 2C. The plot shows that infants of women who took IFA supplements earlier in pregnancy had greater reductions in risk of death of children <5 y of age (P < 0.001; Cox-Mantel-Armitage test for trend). Compared with children of women who did not use IFA supplements, children whose mother consumed 1–29 supplements during pregnancy had a nonsignificant 20% reduction in risk of death of children <5 y of age (aHR: 0.80; 95% CI: 0.61, 1.04; P = 0.096), but children of women who consumed ≥120 supplements had a significant 44% reduction in risk of death of children <5 y of age (aHR: 0.56; 95% CI: 0.37, 0.86; P = 0.008).
women who started taking supplements in third trimester (aHR: 0.74; 95% CI: 0.57, 0.97; \( P = 0.032 \)) to a 38% reduction for women who started taking supplements in the first trimester (aHR: 0.62; 95% CI: 0.49, 0.78; \( P < 0.001 \)).

The effects on risk of death of children <5 y of age of different total numbers of IFA supplements consumed during pregnancy by the timing of the start of supplementation are shown in Figure 3. In women who started taking IFA supplements in the first trimester, there was a progressively greater reduction in risk of death of children <5 y of age as the total number of supplements consumed increased (\( P < 0.001 \); Cochran-Armitage test for trend) that started from a 36% reduction for women who consumed 1–89 supplements (aHR: 0.64; 95% CI: 0.50, 0.82; \( P < 0.001 \)) to a 56% reduction for women who consumed \( \geq 120 \) supplements (aHR: 0.44; 95% CI: 0.28, 0.69; \( P < 0.001 \)). For women who started to use IFA supplements in the second or third trimester, there was no dose-response effect of higher numbers of IFA supplements consumed (\( P = 0.188 \); Cochran-Armitage test for trend), and overall, the reduction in risk was lower than for women who started taking supplements in the first trimester.

With assumption of a causal association between IFA supplements and deaths of children <5 y of age in the pooled data, 14% of deaths of children <5 y of age in Indonesia were attributed to the lack of any use of IFA supplementation during pregnancy (PAR: 0.14; 95% CI: 0.07, 0.22). PAR was highest in the 1997 survey (PAR: 0.14; 95% CI: 0.04, 0.24) but decreased to 10% in the 2007 survey (PAR: 0.10; 95% CI: -0.03, 0.26), although these differences were not statistically significant. Finally, 36% of deaths of children <5 y of age in Indonesia were attributed to failure to use \( \geq 90 \) supplements starting in the first trimester of pregnancy (PAR: 0.36; 95% CI: 0.16, 0.51).

DISCUSSION

Main findings and their significance

IFA taken during pregnancy significantly reduced risk of neonatal deaths (0–30 d) by 39%, infant deaths (0–11 mo) by 34%, and deaths of children <5 y of age by 34% after adjustment for potential confounders including the use of other perinatal health services. Supplementation was also protective for child
A Neonatal Deaths

B Under Five-Year Deaths

FIGURE 1. Plots of adjusted cumulative mortality for neonatal mortality (A) and deaths of children <5 y of age (Under Five-Year Deaths) (B) by use of iron-folic acid supplementation during pregnancy, Indonesia, 1994–2007. Results of the Cox proportional hazards regression analysis were adjusted for the duration of recall period at interview, year of the child’s birth, child sex, region of residence, average coverage of measles vaccination in cluster, household wealth index, maternal age at childbirth, maternal education, parental occupation, maternal marital status, intention to become pregnant, any use of antenatal care from a health professional, delivery mode, place of delivery, type of birth attendant, delivery complications, combined birth rank and interval, combined birth size and timing of delivery, and if ever breastfed. A: On the basis of the model presented in Table 3 for neonatal mortality (adjusted HR: 0.61; 95% CI: 0.43, 0.86; P = 0.005), B: On the basis of the model presented in Table 3 for mortality in children <5 y of age (adjusted HR: 0.66; 95% CI: 0.53, 0.81; P < 0.001).

Iron in pregnancy reduces deaths of children <5 y of age

Deaths in the mutually exclusive time periods examined, although with a progressive decline in the level of protection with the increasing age of the child. The greatest protection was for the first day of life, for which supplementation significantly reduced risk of death by 60%. This effect extended throughout the remaining neonatal period from days 1–30 (31% reduction) and into the postneonatal period from 1–11 mo (26% reduction), but the protective effect was not significant for the 1–4-y-old group.

This study extended earlier findings that the use of IFA in pregnancy significantly reduced risk of early neonatal deaths by 47% after adjustment for potential confounders (17). We showed that the protective effects of supplementation extended beyond the neonatal period to at least the first year of life. We also showed a strong dose-response with risk of death progressively decreasing as the total number of supplements consumed increased. This dose-response effect was mainly shown in women who started their supplementation in the first trimester of pregnancy.

Although there are international policy recommendations for IFA supplementation in pregnancy (30), programs to put these in place are often given a low priority and are poorly implemented. Our findings add an important motivation for strengthening supplementation programs, especially those that start in early pregnancy, because of their potential to accelerate declines in neonatal, infant, and young child mortality and to help countries reach their child-survival Millennium Development Goal.

Our findings were consistent with a trial from China (9), which reported a 54% reduction in early neonatal death (days 0–7) in infants whose mothers had received IFA supplementation during pregnancy compared with the receipt of folic acid alone. Although we did not report early neonatal mortality in this study, our finding of a 60% reduction in neonatal deaths on the first day of life was consistent with the results from China. Also, in our study, the greatest protection for deaths of children <5 y of age was in mothers who started supplementation in the first trimester and who consumed >90 supplements. Similarly, in China, the infants of women who started taking supplements in the first trimester of pregnancy had greater reductions in neonatal mortality than did infants of women who started taking supplements later (31). In Nepal, follow-up of children in a cluster-randomized, double-blinded trial of 4 different combinations of micronutrient supplements in pregnancy showed that maternal IFA supplementation reduced mortality between birth and 7 y of age by 31% (15). We showed similar long-term benefits for survival of children <5 y of age.

Biological mechanisms

The mechanism by which IFA supplementation improves child survival is not known. We showed a progressive decline in the protective effect from immediately after birth through the first year of life, which suggested that improved birth outcomes such as low birth weight and preterm delivery and reduced birth asphyxia might account for improved survival. We have previously reported that significantly fewer smaller-than-average infants were born to mothers who received supplementation (17). Also, in China, IFA supplementation, especially when started in the first trimester, significantly reduced low birth weight and early preterm delivery (31).

In low- and middle-income countries, especially in those settings with limited health care services, preterm delivery is one of the main contributors to neonatal mortality. In India, about one-third of deaths on the first day of life are from birth asphyxia or injury, one-quarter of deaths are from preterm birth, and one-third of deaths are from preterm birth in days 1–6 (32). A WHO calcium-supplementation trial showed that preterm delivery accounted for 62% of early neonatal deaths (14). Likewise, in a cohort of low-birth-weight newborns in Bangladesh, 75% of neonatal deaths were attributed to preterm delivery (13).

Increased infant iron stores may contribute to reduced mortality of children <5 y of age, but direct iron supplementation to children aged 1 to 36 mo in a large trial in Nepal showed no impact on childhood mortality, which suggested that infant iron stores after birth are not critical in reducing deaths (33).
Potential impact on child survival

We calculated PAR to estimate the potential impact of iron supplements in pregnancy on mortality of children <5 y of age. Our estimates indicated that an increase in the use of ≥90 IFA supplements starting in early pregnancy has the potential to prevent 36% of deaths of children <5 y of age in Indonesia. The first assumption that underpinned the estimate of PAR was that the association between IFA supplementation and child mortality is causal. In support of this assumption are the findings of a recent large trial in China that reported a 54% greater reduction in early neonatal mortality in neonates whose mothers received IFA supplements than in neonates whose mothers received folic acid alone (9). We have also shown similar mortality sparing from the use of iron in pregnancy in observational epidemiologic studies from Indonesia (17) and Africa (34). The second assumption was that the removal of IFA supplementation would have no effect on the distributions of other risk factors for mortality of children <5 y of age. This seemed a reasonable assumption for the factors examined in this study, such as the place of delivery, type of birth attendant, and sociodemographic characteristics.

We showed that a remarkably high percentage of women in Indonesia commenced IFA supplementation in the first trimester of pregnancy (53% in pooled data), although only 18% of women consumed a total of ≥90 supplements (Table 1; Figure 3). In Indonesia, an increase in the percentage of women who take ≥90 IFA supplements starting from the first trimester would lead to a substantial reduction in neonatal and infant deaths.

Strengths and limitations

An important strength of this study was the use of nationally representative surveys, with a sample size large enough to provide power to examine the modifying effects of different supplement doses and the timing of the start of supplementation. Data from each survey were derived from similar core questionnaires and collected in a similar manner with robust quality-control methods (19–21). The validity of the results derived from the appropriate timing sequence in the IDHS birth-history information used for which the mothers recalled their most recent birth within the previous 5 y and the use of services during pregnancy, which thus provided information about key antecedent exposures. The restriction of recall to the most recent birth minimized the recall bias (22, 35, 36).

A limitation of our analyses was that both key exposures and outcomes were based on maternal recall, and there was no...
validation of the information provided. However, child mortality is a core measure in IDHS data, and the methods used have been progressively developed for >25 y and shown to be reliable (37). Although the analyses adjusted for many confounding factors, mothers who took IFA were not randomly assigned, and a limitation of the study is the possibility of remaining residual confounding that was not adjusted in the analyses. IFA use was based on maternal recall, and we were not able to validate this information with measurements of iron status. Furthermore, the recall of mothers of the number of IFA supplements consumed during pregnancy might not have been accurate and may have led to a misclassification of the women on the basis of categories of the number of supplements used.

Child survival was only collected from women who survived pregnancy, which may have led to a small underestimate of infant and child mortality (22). Another limitation was the restriction that only information available in the IDHS could be used (eg, the use of postnatal care services was only available in 2002–2003, which precluded use in analyses). Also, some potential predictors of child mortality, such as the anthropometric status of young children, were not collected. Overall these limitations, although important to recognize, were unlikely to have had an important influence on the validity of our results.

In conclusion, we showed that antenatal IFA supplement use significantly protected children <5 y of age from death. The magnitude of this mortality sparing was greatest on the first day of life and progressively decreased with the increasing age of the child. The greatest mortality sparing was in women who started supplementation in the first trimester of pregnancy and took ≥90 supplements during pregnancy. IFA supplementation early in pregnancy and the sustained use until delivery should be strongly supported by programs to reduce deaths of children <5 y of age in low- and middle-income countries.

We are indebted to the Measure Demographic and Health Survey for providing all of Demographic and Health Survey data used in this analysis. The authors' responsibilities were as follows—MJD: designed the study, performed the data analysis, prepared the manuscript, and is the guarantor; CRT: contributed to the design of the study and data analysis and reviewed the manuscript; KA and Cd'E: provided data analysis advice and revision of the manuscript; and all authors: had full access to all study data, including statistical reports and tables, and take responsibility for the integrity of data and accuracy of the data analysis. None of the authors had a conflict of interest.

REFERENCES