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Complete List of Authors:	Upadhyay, Ravi Martines, Jose; Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway Taneja, Sunita; Centre for Health Research and Development, Society for Applied Studies Mazumder, Sarmila; Centre for Health Research and Development, Society for Applied Studies Bahl, Rajiv; World Health Organization, Medicine Bhandari, Nita; Society for applied studies, Centre for Health Research and Development Dalpath, Suresh; National Health Mission, Haryana Bhan, Maharaj; Indian Institute of Technology (IIT), New Delhi, India; Knowledge Integration and Translational Platform (KnIT), Biotechnology Industry Research Assistance Council (BIRAC), New Delhi, India
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TITLE PAGE

Low birth weight contributes to poor outcomes during infancy, even beyond the neonatal period: findings from rural Haryana, India

Ravi Prakash Upadhyay, MD [1], Jose Martines, PhD [2], Sunita Taneja PhD [1], Sarmila Mazumder PhD [1], Rajiv Bahl PhD[3] ,Nita Bhandari PhD[1], Suresh Dalpath MPH[4], Maharaj Kishan Bhan, MD [5,6]

1. Center for Health Research and Development, Society for Applied Studies, New Delhi
2. Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway
3. Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland
4. National Health Mission, Haryana
5. Indian Institute of Technology (IIT), New Delhi, India
6. Knowledge Integration and Translational Platform (KnIT), Biotechnology Industry Research Assistance Council (BIRAC), New Delhi, India

Corresponding author: Dr. Ravi Prakash Upadhyay, Research Scientist, Center for Health Research and Development, Society for Applied Studies, Kalu Sarai, New Delhi, Pin-110016

E-mail: ravi.upadhyay@sas.org.in

Phone number: +911146043751

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Abbreviations

LBW- Low Birth Weight

LMICs- Low and Middle Income Countries

NBCC- Newborn Care Corner

NBSU- Newborn Stabilization Unit

SNCU- Special Newborn Care Unit

WHO- World Health Organization

ORS- Oral Rehydration Salt

RR- Risk Ratio

PAR- Population Attributable Risk

ASHA- Accredited Social Health Activist

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Contributor's statement page

Dr. Ravi conceptualized the study, did the formal analysis, drafted the manuscript
Dr Jose conceptualized the study, helped in analysis and preparation of the manuscript
Dr. Rajiv conceptualized the study, helped in the formal analysis and reviewed and revised the manuscript
Dr. Sunita, Dr. Sarmila, Dr. Nita and Dr. Suresh provided overall coordination and supervised data procurement; provided inputs in the analysis, manuscript writing and critically reviewed the manuscript
Dr. M.K Bhan conceptualized the study, helped in framing the plan of analysis and provided critical feedbacks throughout the analysis and manuscript preparation

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: Low birth weight (LBW) is a risk factor for neonatal mortality and morbidity. It is important to examine whether this risk persists beyond neonatal period. The current analysis aimed to examine association between birth weight and mortality, hospitalization and breast feeding practices during infancy.

Design: Data from a large randomized controlled trial of neonatal vitamin A supplementation (Neovita) trial were used. Log binomial model was applied to assess association between birth weight and mortality, hospitalization rates and breastfeeding practices.

Setting: Rural Haryana, North India

Participants: Newborns recruited in the primary intervention trial that aimed to evaluate the effect of single dose vitamin A supplementation on mortality in the first 6 months of life.

Results: We recruited a total of 44,984 infants, of which 10,658 (23.7%) were born LBW i.e. birth weight less than 2500 grams. In the neonatal period, LBW babies had 4 times higher risk of mortality (RR 3.92; 95% CI, 3.33-4.66) compared with normal birth weight babies. In the post-neonatal period, the risk was two times higher (RR 1.92; 95% CI, 1.71-2.15); even higher in those with birth weight <2000 grams (RR 3.38; 95% CI, 2.71-4.12). The risk of hospitalization in the neonatal period and post-neonatal period was (RR 1.86; 95% CI, 1.64-2.11) and (RR 1.13; 95% CI, 1.05-1.21) respectively. LBWs were at increased risk of delayed initiation of breastfeeding (RR 1.64; 95% CI, 1.45-1.81), no breastfeeding at 6 months (RR 1.34; 95% CI, 1.23-1.46) and at 12 months of age (RR 1.24; 95% CI, 1.18-1.30).

Conclusions: LBW babies, especially with <2000 grams, were at increased risk of mortality, hospitalization and sub-optimal breastfeeding practices during infancy and require additional care beyond the first 28 days of life.

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Key words: Low birth weight; infant mortality; post-neonatal mortality; hospitalization risk; breastfeeding practices; extended home visitation; care and support; India

Strengths and limitations of the study

- Robust population based surveillance system, low loss to follow up and large sample size.
- Birth weight measured by trained study team, thereby reducing chances of misclassification
- Findings are generalizable to large parts of Southeast Asia because of similar social, economic, and demographic features.
- Main trial did not include very sick babies; 36% of which were low birth weight. Excluding them may have made the estimates, especially for mortality, more conservative.
- Lack of reliable data on gestational age restricted analysis by prematurity and intrauterine growth retardation

INTRODUCTION

Approximately 15% of infants in low and middle income countries (LMICs) are born low birth weight (<2500 grams). [1] In 2010, in LMICs, an estimated 18 million infants were born with low birth weight, of which around 7.5 million babies (41%) were born in India alone.[1] Infants with birth weight below 2500 grams face a much greater risk of poor health outcomes such as early growth retardation, infectious diseases, developmental delay and death.[2-5] Recent studies on mortality risk by gestational age of infants in low and middle income countries document high risk of neonatal as well as postneonatal mortality in preterms and small for gestational age infants.[6,7] Existing programs for infant care, globally as well as in India, are heavily investing in improving facility based care for small and sick infants. In India, with the introduction of conditional cash transfer schemes and community awareness interventions delivered through the health system, institutional deliveries have increased to 79%.[8] Newborn care facilities have been established at various levels of public health services. These include newborn care corners (NBCCs) to provide immediate care after childbirth; newborn stabilization units (NBSUs) at community health centers/first referral units for management of selected conditions and to stabilize sick newborns before referral to higher centres; and Special Newborn Care Units (SNCUs) at district/sub-district hospitals to care for sick newborns. [9] Post-discharge from the birth facility, all newborns are to be visited by a community health worker; a total of 6 visits within 42 days of age. These visits aim to promote essential newborn care practices, early detection and special care of preterm and low birth weight infants, early identification of illness and provision of appropriate care and referral. [10] Post 42 days of age, interaction of these infants with the health system is largely dependent on family action, centered around taking the baby for immunization and care seeking for illness. A sustained support to promote survival and growth at household level especially to those born with low birth weight is infrequent, weak and fragmented.

It is important to examine whether child health programs should provide special and more intense surveillance and support beyond 42 days for those with low birth weight. Further, could the additional surveillance and support be directed to a sub-population of LBWs or should it be provided to all low birth weights? The evidence that would compel additional follow up and support should be based on the additional risk of mortality, morbidity, stunting and cognitive deficits in the low birth weights. We believe contemporary data on the outcome of LBW infants for the neonatal and postneonatal period are required to determine if home care program needs to be extended up to 12 months or even 24 months of age. Home care programs cost resources and policy makers require local evidence from recent data on adverse outcomes including mortality rates.

With the aim of adding to the evidence base, we performed a secondary data analysis utilizing the data from an individually randomized, double masked, placebo controlled trial.[11] The primary aim was to examine the relationship between birth weight and mortality outcome in infants born in rural Haryana, India. As a secondary objective, association of birth weight with hospitalization and breastfeeding practices was examined. This information may be helpful to improve the design and intensity of efforts for additional care directed towards low birth weight infants in the post-neonatal period.

METHODS

Study design and setting

We conducted secondary analyses on data from the Neovita trial, a large individually randomized, double-masked, placebo controlled trial of neonatal vitamin A supplementation.[11,12] This study was conducted from June 2010 till July 2012, in Faridabad and Palwal districts in the state of Haryana, North India. The primary aim of the trial was to evaluate the

effect of single dose vitamin A supplementation, given within 72 hours of birth, on mortality in the first 6 months of life. The trial procedures and details of study area have been described in detail elsewhere.[11,12]

Ethical clearance

The trial was approved by the ethics review committees of the Society for Applied Studies, World Health Organization (WHO) and the state government of Haryana. The trial is registered with ClinicalTrials.gov, number NCT01138449. All the concerned investigators of the primary trial gave permission to use the data for this secondary analysis.

Enrolment and data collection

Pregnant women were identified through periodic household surveillance. For each live birth identified, the study team visited the family, explained the trial and screened the infant against pre-defined eligibility criteria (infant aged ≤ 72 hours at screening who could suck or feed and whose family members intended to stay in the study area for at least 6 months). Written consent was obtained from at least one parent i.e. mother or father of the eligible infant. The enrolled infant was weighed by the study team members who were trained and standardized for birth weight measurement. Re-standardization exercises were done very six months. An independent team of study supervisors did random spot checks of all workers once a month and monitored quality of performance.

At enrolment, information was collected on household characteristics (ethnicity, religion, and socio-economic variables to ascertain wealth quintile), infant characteristics (birth weight and sex), birth related characteristics (place of delivery, multiple births, parity) and maternal characteristics (age and education). Infants were visited on the first and third day to document

post supplementation adverse events and to obtain information on the time of breastfeeding initiation in hours after birth (if not already initiated at the enrolment visit) and colostrum intake.

All the eligible infants were enrolled in the trial within 72 hours of birth. Each enrolled infant was followed up till 12 months of age. Infants were contacted when aged 29 days and at 3, 6 and 12 months and at each visit, information was collected or ascertained on feeding practices, hospitalization since last visit and vital status. The study team member asked about what the infant was fed in the previous 24 hours from the time of visit, including breast milk, plain water, animal milk, other fluids, medicines and solid food. A hospitalization was defined as either an inpatient admission (where an infant received an inpatient slip with a registration number and allotted a bed) or a stay of ≥ 6 hours duration in the hospital including the emergency services, diarrhoea management room or any paediatric wards of the institution.

Information on hospitalization was collected through hospital records and documents and in instances where a hospital record could not be found, information provided by the mother was considered. At the first follow up visit at 29 days, data on hospitalization was gathered since the infant was enrolled in the study. For subsequent follow up visits, information on hospitalization was collected since the last follow up visit.

Operational definitions used

Delayed initiation of breastfeeding - was defined as infant being initiated on breastfeeding after an hour of birth (>1 hour after birth).[13] However, for the purpose of analysis, we also considered breastfeeding initiation after 24 hours of birth as an outcome.

Exclusive breastfeeding- defined as infant being given no other food or drink, not even water, except breast milk (including milk expressed or from a wet nurse), with the exception of infant receiving oral rehydration salt (ORS), drops and syrups (vitamins, minerals and medicines) [13]

Outcomes for the secondary analysis

The primary outcome in our analysis was the association between birth weight and mortality during infancy. Secondary outcomes were association of birth weight with hospitalization and breastfeeding practices i.e. early initiation of breastfeeding, exclusive breastfeeding at one and three months of age, and "any breastfeeding" at 6 and 12 months of age.

Data analysis

For the analyses, infants with information on birth weight, vital status, episodes of hospitalization, breastfeeding practices and data on covariates were included. Data analysis was performed using STATA version 11 (Stata Corporation, College Station, TX). The distribution of the data was examined. Proportions were calculated for categorical variables.

For analysis of mortality rates in the neonatal period, all babies recruited in the trial, within 72 hours of birth, were considered. For analysis of mortality between 29 to 90 days of age, 29 to 180 days and 29 to 365 days of age, only infants who were alive at 29 days of age were included in the analysis. Similarly, for analysis of hospitalization in the neonatal period, infants who were recruited within 72 hours of birth and for those on whom data on hospitalization were available were considered. For analysis of hospitalization from 29 to 90 days of age, 29 to 180 days of age and 29 to 365 days of age, only infants who were alive at

29 days and had data on hospitalization within the specified time period were included in the analysis.

For delayed initiation of breastfeeding, infants were included in the analyses only if breastfeeding was initiated. For non-exclusive breastfeeding at 1 and 3 months, only infants alive at 1 month and 3 months of age, respectively, for whom breastfeeding data were available, were included in the analysis. Similarly, for no breastfeeding at 6 and 12 months of age, only infants that were alive at 6 and 12 months and information was available on their breastfeeding status was included in the analysis.

Log binomial model was used to assess the relationship between birth weight and mortality, hospitalization and breastfeeding practices. Birth weight was the exposure of interest and was categorized into ≥2500, 2000-2499 and <2000 grams. Adjustment was done for other covariates that were significant on univariate analysis at a p-value of <0.20.[14,15] Covariates considered were: infant sex, multiple births, maternal age, maternal education, parity, place of delivery, type of delivery, religion, ethnicity, wealth quintile and administration of single dose of vitamin A (intervention in the primary trial). Reliable gestational age data based on ultrasound could not be obtained and therefore, analysis based on prematurity and intrauterine growth retardation could not be conducted. Assessment for effect modification (i.e. potential interaction) between birth weight and all covariates was done using an interaction term in the model. Likelihood ratio test was used to compare models with or without the interaction term. Population attributable risks were calculated against each birth weight category for each of the three outcomes i.e. mortality, hospitalization and breastfeeding practices across the different age ranges. Population attributable risks were calculated using the following formula: $P_{pop} * (RR-1)/[P_{pop} * (RR-1) + 1]$; where P_{pop}= proportion of exposed subjects in the study population and RR= risk ratio.[15,16]

RESULTS

Characteristics of the study population

Figure 1 shows the overall flow of study participants in the primary trial. A total of 44,984 infants were recruited within 72 hours of birth, of which 65% were enrolled within 24 hours of birth. The characteristics of the population are presented in Table 1. Out of the enrolled infants, 10,658 (23.7%) weighed <2500 grams. The mean birth weight (SD) was 2732.9 (420.1) grams. Majority (86.1%) of the mothers were 20-30 years old. Mean (SD) age of mothers was 23.9 (4.1) years. Close to half the mothers were illiterate (41.8%) and majority of the infants belonged to Hindu families (76.9%). Nearly half the infants were born at home (43.3%); a third of the mothers were primiparous (32.7%) and around half of the infants were males (52.1%). Almost all mothers delivered a single infant (98.7%).

Association of birth weight with mortality during infancy

Table 2 shows the association between birth weight and mortality during the first year of life. After adjustment for covariates, being born with low birth weight, especially with a birth weight of less than 2000 gram, was associated with higher risk of mortality compared to normal birth weight infants during the whole infancy. In the neonatal period, those with birth weight between 2000-2499 grams had around 2.5 fold higher risk of death (RR 2.56; 95% CI, 2.13-3.12) while those with <2000 grams had 16 times higher risk (RR 15.64; 95% CI, 12.90-19.44). After the neonatal period, this increased risk of death in LBWs was observed between 29 to 90 days of age (RR 2.14; 95% CI, 1.74-2.58), 29 to 180 days of age (RR 2.08; 95% CI, 1.77-2.36) and 29 to 365 days of age (RR 1.92; 95% CI, 1.71-2.15). In context of mortality, the population attributable risk (PAR) for low birth weight was as high as 41% in the neonatal period and 17.6% for the post neonatal period till end of infancy.

Association of birth weight with severe morbidity during infancy

In the neonatal period, low birth weight infants were at an increased risk for hospitalization (RR 1.86; 95% CI, 1.64-2.11) compared to normal birth weight infants after adjustment for all potential covariates. This increased risk was observed in infants with birth weight between 2000 to 2499 grams (RR 1.73; 95% CI, 1.52-1.98) and was higher among those <2000 grams (RR 3.13; 95% CI, 2.45-3.99) (Table 3). For the rest of infancy, although LBW infants remained at an increased risk of hospitalization, this risk was largely driven by infants <2000 grams. Overall, the relative risk of hospitalization between 29 to 365 days of age was 1.13 (95% CI, 1.05-1.21) in LBW infants and for those with birth weight <2000 grams was 1.74 (95% CI, 1.46-2.06). The population attributable risk for hospitalization in LBWs was around 17% in the neonatal period and reduced to only 3% in post-neonatal period till 365 days of age (Table 3).

Association of birth weight with breastfeeding practices

Overall, close to two-thirds of LBW babies (65.9%) had delayed initiation of breastfeeding i.e. after one hour of birth. Majority of LBW babies (63.7%) were not exclusive breastfed by one and even more (78.2%) by three month of age (Table 4). At 6 and 12 months, around 8% and 18% of LBW infants were not at all breastfed, respectively. Sub-optimal breastfeeding practices were significantly associated with lower birth weight, especially with a birth weight of <2000 grams, after adjustment for all possible confounding variables (Table 4). Compared to infants with normal birth weight, those with birth weight of <2500 grams had a slightly higher risk of initiating breastfeeding after 1 hour of birth (RR 1.03; 95% CI, 1.01-1.06) and a substantially higher risk of initiating after 24 hours of birth (RR 1.64; 95% CI, 1.45-1.81).

A higher risk of non-exclusive breastfeeding at one (RR 1.07; 95% CI, 1.02-1.15) and three (RR 1.08; 95% CI, 1.03-1.14) months was observed only in infants with birth weight of

<2000 grams. LBW infants were at a much higher risk of not being breastfed at all, compared to normal birth weight infants, at six months (RR 1.34; 95% CI, 1.23-1.46) and twelve months (RR 1.24; 95% CI, 1.18-1.30) of age. The risk was higher in infants with birth weight of less than 2000 grams i.e. (RR 1.49; 95% CI, 1.20-1.86) at 6 months and (RR 1.36; 95% CI, 1.18-1.56) at 12 months of age. The PAR for sub-optimal breastfeeding practices in LBW infants was around 13.3% for initiation of breastfeeding beyond 24 hours of birth; 7.2% for no breastfeeding at 6 months and 5.1% for no breastfeeding at 12 months of age.

DISCUSSION

This secondary data analysis showed that in low birth weight infants, compared to those with normal birth weight, mortality in the neonatal as well as in the post neonatal period till 1 year of age was substantially higher. The PAR for mortality in low birth weight infants was highest in the neonatal period and declined at 12 months of age. The risk for hospitalization, reflecting severe morbidity, in both <2000 and 2000-2499 gram babies was higher compared to normal birth weight infants in the neonatal period; in post-neonatal period, the excess risk was seen only in <2000 gram infants. However, the PAR for hospitalization was relatively small. The risk of delayed initiation of breastfeeding and early termination of breastfeeding, both at 6 and 12 months of age was higher in the low birth weight group but the strength of association was substantially greater for those below 2000 grams. The PAR for delayed initiation of breastfeeding was around 13%. An additional 7% and 5% of "continued breastfeeding" rates at 6 and 12 months respectively could be potentially achieved by focusing on promoting breastfeeding practices in low birth weight infants, beyond the neonatal period. Achieving even this much magnitude of benefit in appropriate breastfeeding practices is crucial as early initiation of breastfeeding and continued breastfeeding during the

first year of life and particularly in early infancy has been shown to be associated with improved survival and lesser morbidity. [18,19] This is strikingly so in developing country setting.

The findings of the study corroborate well with the previously published literature from low and middle income countries. Katz J et al in their pooled analysis, utilising data from 20 cohorts from Asia, Africa and Latin America, documented the risk of post-neonatal mortality in preterm (RR 2.50; 95% CI, 1.48 – 4.22) and small for gestational age (RR 1.90; 95% CI, 1.32 – 2.73) infants to be similar to what we have observed in the current analysis. [7] A cohort study of low birth weight infants and their health outcomes in the first year of life from rural Ghana also found increased risk of mortality in low birth weight infants in the post-neonatal period compared to non-low birth weight infants. [20] Also, the risk of illness in LBW infants, compared to normal birth weight infants, declined in the post-neonatal period, similar to what the current analysis documents. [20]

In the same dataset we have also observed that low birth weight infants were at an increased risk of delay in receiving vaccination and incomplete immunization by the end of infancy. Less than one-third (29.7%) of LBW infants were fully immunized by one year of age and proportion with delayed vaccination for DPT1 and DPT3 was 52% and 81% respectively. [21] In India, a little more than one-fourth of the babies are born with low birth weight.[22] The proportion of LBW varies by states and ranges from 22% to 36%.[23] Continued and quality care of small and sick babies is a priority issue to improve survival as well as thriving of this vulnerable subset of infants. Health facilities have provision for care of small and sick infants and the home visitation programme until 42 days of age aims to improve neonatal survival and reduce morbidities, although achieving adequate quality and coverage for these neonatal interventions is a persistent challenge. [9,10]

An important issue is to decide whether support through health care provider-family interactions is sufficiently beneficial to be extended well into the post-neonatal period and, if so, how it should be designed. An additional question of relevance is whether post neonatal surveillance and support through continued home visitation by health care providers should be for all infants or restricted to low birth weights. Our data suggests that the extended follow up for low birth weight infants should ideally be continued till the end of infancy owing to the high risk of mortality, hospitalization and sub-optimal breastfeeding practices. However in low resource settings, from the perspective of mortality reduction, the follow up should be at least till the first three months of life as it would provide the maximum reward in terms of proportion of LBWs to be cared for (23.2%) and the corresponding reduction in mortality (PAR of 21%). The follow up for those less than 2000 grams could potentially be extended till the end of infancy as they constitute a small proportion of infants (2.5%) and corresponding reduction in mortality would be 5.6%. The extended follow up would be particularly beneficial in areas where post-neonatal mortality is high. Since, wasting and stunting are also highly prevalent in India and particularly in those born with low birth weight there is a case for interventions in most parts of the country. [24-26] The package of intervention could constitute monthly home visits, counselling on optimal infant care practices, lactation support, growth monitoring, promoting timely immunization, recognition of illness and prompt care seeking and advice on appropriate complementary feeding. Such a package of interventions is expected to reduce incidence and severity of illness and improve survival, growth and development. In addition, they would lead to lower health care costs particularly out of pocket expenses by the family as in many parts of India, private care providers are commonly used and leads to high out of pocket expenses. [27,28]

The current program during the neonatal period targets all neonates which is appropriate. Our findings suggest the need for increasing the duration of contacts for the LBWs. There should

be focus on improving the quality of these health care provider-family interactions and follow up action when merited. The current situation where immunization is the only available contact with LBW, in the post neonatal period, leaves a large proportion of LBW infants vulnerable to premature death or poor growth and development. There is an imminent need for strengthening the existing mechanism of care and support for newborns in the first 42 days of life along with introducing additional care for LBW infants through a dedicated home based programme throughout the first year of life. Availability of Accredited Social Health Activist (ASHA) who works closer to home gives a unique opportunity to design a programme linking facility to home. [29]

An informed decision whether to focus on all infants must take into account the population attributable risk (PAR) for other adverse outcomes such as stunting. Overall, in areas of high mortality during infancy and high stunting rates, a case can be made for extended home contacts for infants beyond the neonatal period. Whether the cost-benefits may be greater and the feasibility increased by focusing such programs on LBW infants and specific health interventions are important aspects to consider.

Strength and limitations

The findings of current analysis have adequate generalizability as the social, economic, and demographic features of the study setting are fairly representative of large parts of Southeast Asia. The strengths of the study include robust population based surveillance system, low loss to follow up and large sample size. Also, for each of the outcomes considered in the analysis, data were available for >98% of the infants, reducing the risk of selection bias. All the infants were recruited within 72 hours of birth and their weight was measured by trained study team, thereby reducing chances of misclassification of infants by birth weight. In order

to achieve adequate quality of data, the study team members were rigorously trained and underwent periodic inter and intra observer standardization exercises.

A limitation that must be considered while interpreting the findings is that the main trial did not include very sick babies, i.e., those that were unable to feed in the first 72 hours. To assess whether infants who were not enrolled in the study (i.e. those who died before contact for screening, those who could not be enrolled because of serious illness, or those who were admitted in intensive care) were of low birth weight, attempt was made to obtain birthweights for all infants who were screened but not enrolled. Weights were obtained by study workers at the visit to assess eligibility for screening. Out of the 2793 infants excluded, weights for 2087 was obtained and of these infants, 748 (36%) were low birthweight. In such babies, inadequate breastfeeding practices, morbidity and mortality would probably have been higher. Excluding them, therefore, may have made our estimates more conservative. We could not obtain reliable data on gestational age, making it impossible to assess how the outcomes might have been influenced by prematurity.

Conclusion

Low birth weight infants experience high risk of mortality, hospitalization and sub-optimal breastfeeding practices even beyond the neonatal period and therefore require continued care and support through health system in order to promote their survival. The current mechanism of home visitation program in India that focuses on the first 42 days of life may need to be extended to at least cover the first three months of infancy and if resources permit, till end of infancy.

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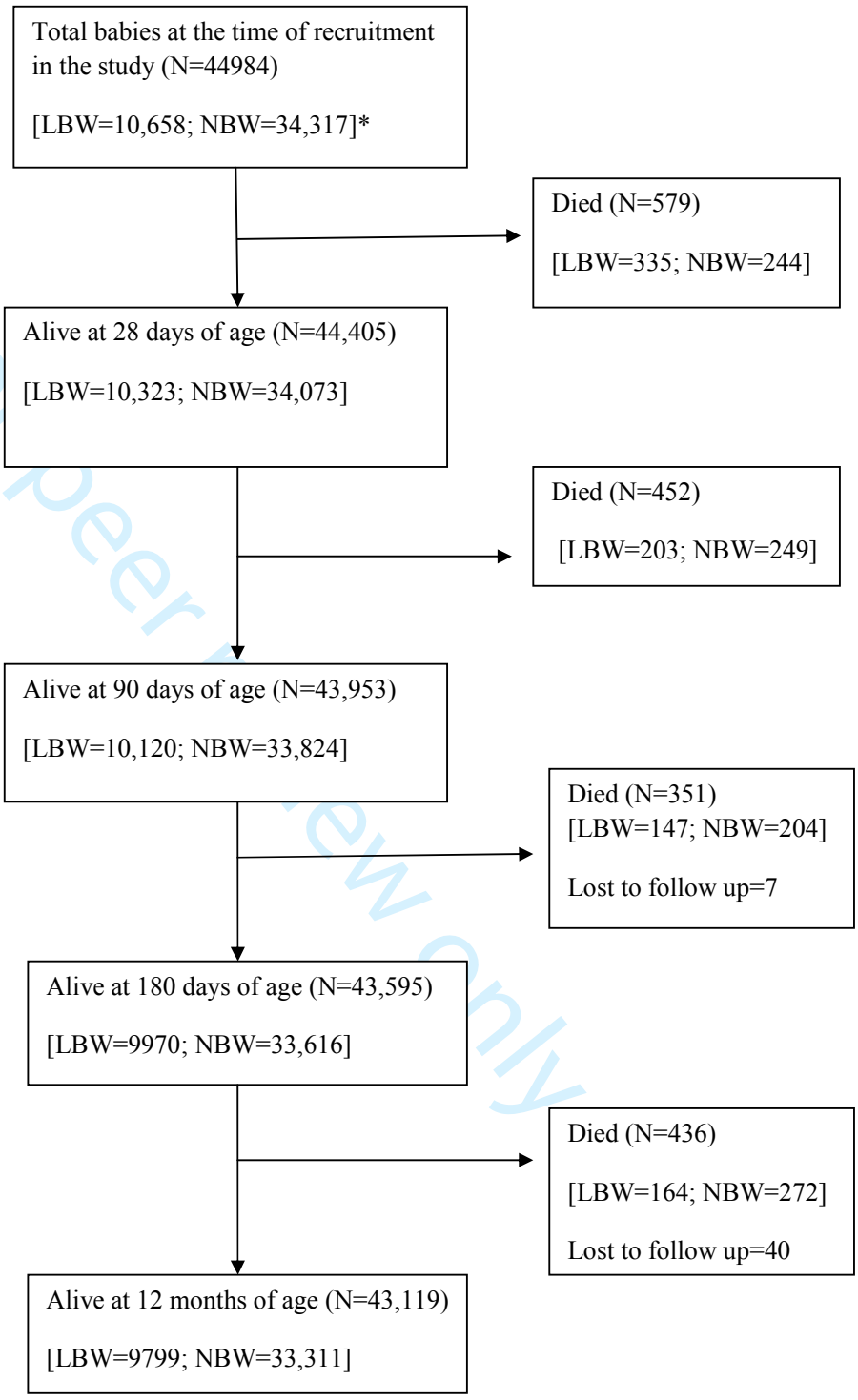
Figure 1 . Overall flow of infants recruited in the primary trial



*LBW- Low birth Weight; NBW- Normal birth weight; 9 infants had data missing on birth weight

Table 1. Baseline characteristics of infants randomized in the primary trial (N=44,984)

Variables	n (%)
HOUSEHOLD CHARACTERISTICS	
Religion	
Hindu	34573 (76.9)
Muslim	9906 (22.0)
Others¶	505 (1.1)
Ethnicity**	
General	12041 (26.8)
Other Backward Class (OBC)	21892 (48.7)
Scheduled Caste/Tribe (SC/ST)	11051 (24.5)
MATERNAL CHARACTERISTICS	
Mother's age (in years)	
<20	3563 (8.0)
20-30	38747 (86.1)
>30	2674 (5.9)
Mother's education (Years of schooling)	
Illiterate (0)	18814 (41.8)
1 to ≤9	16667 (37.1)
10 to <12	4383 (9.7)
≥12	5120 (11.4)
BIRTH RELATED CHARACTERISTICS	
Place of delivery*	
Home	19478 (43.3)
Government facility	14136 (31.4)
Private facility	11326 (25.2)
Type of delivery	
Normal	42210 (93.8)
Caesarean	2592 (5.8)
Assisted	182 (0.4)
Singleton	44413 (98.7)
Multiple	571 (1.3)
Parity	
Multiparity	30257 (67.3)
Primiparity	14727 (32.7)
INFANT CHARACTERISTICS	
Sex of the baby	
Male	23418 (52.1)
Female	21566 (47.9)
Birth weight (in grams)†	
≥2500	34317 (76.3)
2000-2499	9403 (20.9)
<2000	1255 (2.8)

¶ others- Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist; **General- group that do not qualify for any of the positive discrimination schemes by Government of India (GOI), OBC- term used by the Government of India to classify castes which are socially and educationally disadvantaged, SC/ST- official designations given to groups of historically disadvantaged indigenous people in India; *remaining 44 births took place on way to health facility; † 9 infants had data missing on birth weight

Table 2. Association of mortality rates in the first year of life by birth weight in infants from rural Haryana, North India

	Number of deaths (rate per 1000 live births	Number of infants**	Univariate	Multivariate§	PAR (%)
			RR (95% CI)	RR (95% CI)	
Neonatal mortality (from enrolment to 28 days)					
Total number	---	44975			
Birth weight (grams)					
>=2500	244 (7.1)	34,317 (76.3)	Ref	Ref	-----
<2500	335 (31.4)	10658 (23.7)	4.42 (3.78-5.23)	3.92 (3.33-4.66)	41
2000-2499	181 (19.2)	9403 (20.9)	2.71 (2.27-3.31)	2.56 (2.13-3.12)*	24.6
<2000	154 (122.7)	1255 (2.8)	17.28 (14.22-20.89)	15.64 (12.90-19.44)*	29.1
Post Neonatal mortality (29-90 days)					
Total number	----	44396			
Birth weight (grams)					
>=2500	249 (7.3)	34073 (76.8)	Ref	Ref	-----
<2500	203 (19.7)	10323 (23.2)	2.69 (2.21-3.19)	2.14 (1.74-2.58)	21
2000-2499	126 (13.7)	9222 (20.7)	1.88 (1.51-2.33)	1.68 (1.36-2.08)*	12.3
<2000	77 (69.9)	1101 (2.5)	9.57 (7.32-12.07)	6.43 (4.69-8.34)*	11.9
Post Neonatal mortality (29-180 days)					
Total number	----	44396			
Birth weight (grams)					
>=2500	453 (13.3)	34073 (76.8)	Ref	Ref	-----
<2500	350 (33.9)	10323 (23.2)	2.55 (2.21-2.93)	2.08 (1.77-2.36)	20
2000-2499	249(27.0)	9222 (20.7)	2.01 (1.72-2.34)	1.78 (1.52-2.09)*	13.9
<2000	101 (91.7)	1101 (2.5)	6.89 (5.47-8.36)	4.24 (3.28-5.37)*	7.5
Post Neonatal mortality (29 to 365 days)					
Total number	---	44396			
Birth weight (grams)					
>=2500	725 (21.3)	34073 (76.8)	Ref	Ref	---
<2500	514 (49.8)	10323 (23.2)	2.33 (2.07-2.58)	1.92 (1.71-2.15)	17.6
2000-2499	392 (42.5)	9222 (20.7)	1.99 (1.76-2.24)	1.76 (1.54-1.99)	13.6
<2000	122 (110.8)	1101 (2.5)	5.20 (4.34-6.16)	3.38 (2.71-4.12)	5.6

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, ethnicity, wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial); ** 9 infants had data missing on birth weight; *statistical significance at p-value<0.05; PAR- population attributable risk

Table 3. Association of hospitalization for severe morbidity in the first year of life, by birth weight in infants from rural Haryana, North India

	Infants with ≥1 episode (s) of hospitalization (%)	Number of infants**	Univariate	Multivariate§	PAR (%)
			Unadjusted RR (95% CI)	Adjusted RR (95% CI)	
Hospitalization from enrolment to 28 days					
Total number	---	44481			
Birth weight (grams)					
>=2500	724 (2.13)	34028 (76.5)	Ref	Ref	-----
<2500	383 (3.66)	10453 (23.5)	1.72 (1.51-1.93)	1.86 (1.64-2.11)*	16.8
2000-2499	311 (3.35)	9273 (20.8)	1.57 (1.37-1.78)	1.73 (1.52-1.98)*	13.2
<2000	72 (6.10)	1180 (2.7)	2.89 (2.27-3.63)	3.13 (2.45-3.99)*	5.4
Hospitalization in post neonatal period (29-90 days)					
Total number	---	43820			
Birth weight (grams)					
>=2500	582(1.73)	33674 (76.8)	Ref	Ref	-----
<2500	201 (1.98)	10146 (23.2)	1.15 (0.98-1.35)	1.20 (1.02-1.42)*	4.4
2000-2499	161(1.78)	9076 (20.7)	1.03 (0.87-1.22)	1.11 (0.93-1.33)	2.2
<2000	40 (3.74)	1070 (2.5)	2.17 (1.58-2.97)	2.11 (1.50-2.95)*	2.6
Hospitalization in post neonatal period (29-180 days)					
Total number	---	43056			
Birth weight (grams)					
>=2500	1444 (4.35)	33198 (77.1)	Ref	Ref	---
<2500	469 (4.76)	9860 (22.9)	1.09 (0.98-1.21)	1.15 (1.03-1.27)*	3.3
2000-2499	376 (4.24)	8863 (20.6)	0.97 (0.87-1.09)	1.05 (0.94-1.18)	1.0
<2000	93 (9.33)	997 (2.3)	2.14 (1.76-2.62)	2.08 (1.69-2.59)*	2.4
Hospitalization in post neonatal period (29 to 365 days)					
Total number	---	42708			
Birth weight (grams)					
>=2500	3046 (9.23)	32966 (77.2)	Ref	Ref	---
<2500	960 (9.86)	9742 (22.8)	1.07 (1.00-1.14)	1.13 (1.05-1.21)*	2.9
2000-2499	803 (9.17)	8761 (20.5)	0.99 (0.92-1.07)	1.07 (0.98-1.15)	1.4
<2000	157 (16.0)	981 (2.3)	1.73 (1.49-2.01)	1.74 (1.46-2.06)*	1.7

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, ethnicity, wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial), *statistical significance at p-value<0.05; **Denotes the number of infants that were alive at the start point of analysis time frame and had data on hospitalization during the period under

consideration e.g. for analysis of hospitalization between 1 to 6 months of age, only those infants were included in analysis that were alive at 1 month of age and had data on hospitalization between 1 to 6 months of age; PAR- population attributable risk

Table 4 . Association of breastfeeding practices by birth weight in infants from rural Haryana, North India

	Number of infants with outcome of interest (%)	Total no. of infants**	Univariable	Multivariable§	PAR (%)
			RR (95% CI)	RR (95% CI)	
Delayed initiation of breastfeeding (BF initiated after 1 hour of birth)					
Total number	---	40878			
Birth weight (grams)					
>=2500	19906 (64.0)	31090 (76.1)	Ref	Ref	-----
<2500	6457 (65.9)	9788 (23.9)	1.03 (1.01-1.05)	1.03 (1.01-1.06)*	0.71
2000-2499	5685 (65.7)	8654 (21.2)	1.03 (1.01-1.05)	1.04 (1.01-1.06)*	0.84
<2000	772 (68.1)	1134 (2.7)	1.06 (1.02-1.11)	1.07 (1.03-1.15)*	0.19
Delayed initiation of breastfeeding (BF initiated after 24 hours of birth)					
Total number	----	40878			
Birth weight (grams)					
>=2500	1002 (3.2)	31090 (76.1)	Ref	Ref	-----
<2500	497 (5.1)	9788 (23.9)	1.59 (1.41-1.74)	1.64 (1.45-1.81)*	13.3
2000-2499	413 (4.8)	8654 (21.2)	1.49 (1.32-1.65)	1.55 (1.37-1.73)*	10.4
<2000	84 (7.4)	1134 (2.7)	2.31 (1.85-2.84)	2.43 (1.91-3.07)*	3.7
Non-exclusive breastfeeding at 1 month					
Total number	----	43656			
Birth weight (grams)					
>=2500	20491 (61.1)	33541 (76.8)	Ref	Ref	-----
<2500	6446 (63.7)	10115 (23.2)	1.04 (1.03-1.07)	1.03 (0.99-1.05)	0.69
2000-2499	5709(63.1)	9042 (20.7)	1.03 (1.02-1.05)	1.02 (0.98-1.05)	0.41
<2000	737 (68.7)	1073 (2.5)	1.12 (1.08-1.17)	1.07 (1.02-1.15)*	0.17
Non-exclusive breastfeeding at 3 month					
Total number	---	42628			
Birth weight (grams)					
>=2500	25401 (77.2)	32877 (77.1)	Ref	Ref	---
<2500	7630 (78.2)	9751 (22.9)	1.01 (1.00-1.03)	1.01 (0.98-1.03)	0.22
2000-2499	6793 (77.5)	8759 (20.6)	1.00 (0.98-1.02)	1.02 (0.97-1.06)	0.41
<2000	837 (84.4)	992 (2.3)	1.09 (1.07-1.13)	1.08 (1.03-1.14)*	0.19

No breastfeeding at 6 months					
Total number	---	42392			
Birth weight (grams)					
>=2500	1936 (5.91)	32744 (77.2)	Ref	Ref	---
<2500	778 (8.06)	9648 (22.8)	1.36 (1.26-1.49)	1.34 (1.23-1.46)*	7.2
2000-2499	682 (7.86)	8676 (20.5)	1.33 (1.22-1.45)	1.32 (1.21-1.45)*	6.1
<2000	96 (9.87)	972 (2.3)	1.67 (1.37-2.03)	1.49 (1.20-1.86)*	1.1
No breastfeeding at 12 months					
Total number	---	42492			
Birth weight (grams)					
>=2500	4776 (14.5)	32883 (77.4)	Ref	Ref	----
<2500	1791 (18.6)	9609 (22.6)	1.28 (1.22-1.35)	1.24 (1.18-1.30)*	5.1
2000-2499	1572 (18.2)	8642 (20.3)	1.26 (1.19-1.32)	1.23 (1.16-1.30)*	4.5
<2000	219 (22.7)	967 (2.3)	1.57 (1.37-1.78)	1.36 (1.18-1.56)*	0.8

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, ethnicity, wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial); *statistical significance at p-value<0.05; **Denotes the total number of infants for which desired breastfeeding information was available; PAR-population attributable risk

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page no. in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes (Page -3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes (Page -3)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes (Page 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes (Page 5)
Methods			
Study design	4	Present key elements of study design early in the paper	Yes (Page 5-9)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes (Page 5-9)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes (Page 5-9)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Yes (Page 10,21,23-26)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes (Page 5-9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes (Page 5-9)
Bias	9	Describe any efforts to address potential sources of bias	Yes (Page 5-9)
Study size	10	Explain how the study size was arrived at	Yes (Page 5-9)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes (Page 5-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes (Page 5-9)
		(*b*) Describe any methods used to examine subgroups and interactions	Yes (Page 5-9)
		(*c*) Explain how missing data were addressed	Yes (Page 5-9)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Yes (Page 5-9)
		(*e*) Describe any sensitivity analyses	We did a sub group analysis by sub-categories of low birth weight

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes (Page 20)
		(b) Give reasons for non-participation at each stage	Yes (page 10-12; page 20)
		(c) Consider use of a flow diagram	Yes (Page 20)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest	Yes (Page 23-26)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Yes (Page 23-26)
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes (Page 10-12; 23-26)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes (Page 10-12; 23-26)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes (Page 10-12; 23-26)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes (Page 10-12; 23-26)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes (Page 12-16)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes (Page 12-16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes (Page 12-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes (Page 12-16)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes (Page 1)

BMJ Open

Risk of post-neonatal mortality, hospitalization and sub-optimal breastfeeding practices in low birth weight infants from rural Haryana, India: Findings from a secondary data analysis

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TITLE PAGE

Risk of post-neonatal mortality, hospitalization and sub-optimal breastfeeding practices in low birth weight infants from rural Haryana, India: Findings from a secondary data analysis

Ravi Prakash Upadhyay, MD [1], Jose Martines, PhD [2], Sunita Taneja PhD [1], Sarmila Mazumder PhD [1], Rajiv Bahl PhD[3] ,Nita Bhandari PhD[1], Suresh Dalpath MPH[4], Maharaj Kishan Bhan, MD [5,6]

1. Center for Health Research and Development, Society for Applied Studies, New Delhi
2. Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway
3. Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland
4. National Health Mission, Haryana
5. Indian Institute of Technology (IIT), New Delhi, India
6. Knowledge Integration and Translational Platform (KnIT), Biotechnology Industry Research Assistance Council (BIRAC), New Delhi, India

Corresponding author: Dr. Ravi Prakash Upadhyay, Research Scientist, Center for Health Research and Development, Society for Applied Studies, Kalu Sarai, New Delhi, Pin-110016

E-mail: ravi.upadhyay@sas.org.in

Phone number: +911146043751

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Potential conflicts of interest: The authors have no conflicts of interest relevant to this article to disclose

Clinical Trial registry name and registration number: The trial is registered with ClinicalTrials.gov, number NCT01138449.

Data sharing statement: No additional data available. Request for data used in the current analysis can be directed to the corresponding author.

Abbreviations

LBW- Low Birth Weight

LMICs- Low and Middle Income Countries

NBCC- Newborn Care Corner

NBSU- Newborn Stabilization Unit

SNCU- Special Newborn Care Unit

WHO- World Health Organization

ORS- Oral Rehydration Salt

RR- Risk Ratio

PAR- Population Attributable Risk

ASHA- Accredited Social Health Activist

Short running title: Adverse outcomes in low birth weights beyond neonatal period

Word count: 4884 (excluding abstract, figures, tables and references)

Contributor's statement page

RPU conceptualized the study, did the formal analysis, drafted the manuscript
JM conceptualized the study, helped in analysis and preparation of the manuscript
RB conceptualized the study, helped in the formal analysis and reviewed and revised the manuscript
ST, SM, NB and SD provided overall coordination and supervised data procurement; provided inputs in the analysis, manuscript writing and critically reviewed the manuscript
MKB conceptualized the study, helped in framing the plan of analysis and provided critical feedback throughout the analysis and manuscript preparation

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: Low birth weight (LBW) is a risk factor for neonatal mortality and morbidity. It is important to examine whether this risk persists beyond neonatal period. The current secondary data analysis aimed to examine association of birth weight with mortality, hospitalization and breast feeding practices during infancy.

Design: Data from a large randomized controlled trial of neonatal vitamin A supplementation (Neovita) trial were used. Log binomial model was applied to assess association between birth weight and mortality, hospitalization and breastfeeding practices.

Setting: Rural Haryana, North India

Participants: Newborns recruited in the primary intervention trial that aimed to evaluate the effect of single dose oral vitamin A supplementation on mortality in the first 6 months of life.

Results: We recruited a total of 44,984 infants, of which 10,658 (23.7%) were born LBW i.e. birth weight less than 2500 grams. In the neonatal period, LBW babies had 4 times higher risk of mortality (RR 3.92; 95% CI, 3.33-4.66) compared with normal birth weight babies. In the post-neonatal period, the risk was two times higher (RR 1.92; 95% CI, 1.71-2.15); even higher in those with birth weight <2000 grams (RR 3.38; 95% CI, 2.71-4.12). The risk of hospitalization in the neonatal period and post-neonatal period was (RR 1.86; 95% CI, 1.64-2.11) and (RR 1.13; 95% CI, 1.05-1.21) respectively. LBWs were at increased risk of breastfeeding initiation 24 hours after birth (RR 1.64; 95% CI, 1.45-1.81), no breastfeeding at 6 months (RR 1.34; 95% CI, 1.23-1.46) and at 12 months of age (RR 1.24; 95% CI, 1.18-1.30).

Conclusions: LBW babies, especially those with birth weight of <2000 grams, were at increased risk of mortality, hospitalization and sub-optimal breastfeeding practices during entire infancy and therefore require additional care beyond the first 28 days of life.

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Key words: Low birth weight; infant mortality; post-neonatal mortality; hospitalization risk; breastfeeding practices; extended home visitation; care and support; India

Strengths and limitations of the study

- Robust population based surveillance system, low loss to follow up and large sample size.
- Birth weight measured by trained study team, thereby reducing chances of misclassification
- Findings are generalizable to large parts of Southeast Asia because of similar social, economic, and demographic features.
- Main trial did not include babies who either died or were unable to feed in the first 72 hours of birth; 36% of which were low birth weight. Excluding them in the primary trial may have made the estimates, especially for mortality, more conservative.
- Lack of reliable data on gestational age restricted analysis by prematurity and intrauterine growth retardation

INTRODUCTION

Approximately 15% of infants in low and middle income countries (LMICs) are born low birth weight (LBW) (i.e. birth weight <2500 grams). [1] In 2010, in LMICs, an estimated 18 million infants were born with low birth weight, of which around 7.5 million babies (41%) were born in India alone.[1] LBW infants face high risk of poor health outcomes such as growth retardation, developmental delay and death.[2-5] Recent studies on mortality risk by gestational age in LMICs document high risk of neonatal as well as post-neonatal mortality in preterms and small for gestational age infants.[6,7] Existing programs for infant care, globally as well as in India, are heavily investing in improving facility based care for small and sick infants alongside efforts to increase institutional deliveries so that quality care, without delay, could be provided to "at-risk" newborns. In India, with the introduction of government schemes such as Janani Suraksha Yojna (JSK) and Janani Shishu Suraksha Karyakaram (JSSK), a substantial increase in institutional deliveries has occurred.[8,9] According to the recent National Family Health Survey (NFHS-4), the institutional delivery rate for India is 79%.[10] Janani Suraksha Yojana (JSY), a conditional cash transfer scheme was introduced in the year 2005, with a strategy to link cash assistance to institutional delivery.[8,9] Due to JSY, institutional deliveries across the country increased but with a few limitations such as high out of pocket expenditure by families especially for purchase of the drugs and transport. In the view of these limitations, Government of India introduced Janani Shishu Suraksha Karyakram (JSSK) scheme in June 2011.[9] Under this scheme- birth of the baby through normal vaginal delivery, caesarean section, drugs and consumables, diagnostics and transport between home and health facility is provided free of cost.[9]

Newborn care facilities have been established at various levels of Indian public health system. These include newborn care corners (NBCCs) to provide immediate care after childbirth; newborn stabilization units (NBSUs) at community health centers/first referral

units for management of selected conditions and to stabilize sick newborns before referral to higher centres; and Special Newborn Care Units (SNCUs) at district/sub-district hospitals to care for sick newborns. [11] Post-discharge from the birth facility, all newborns are to be visited by a community health worker; a total of 6 visits within 42 days of age. These visits aim to promote essential newborn care practices, early detection and special care of preterm and low birth weight infants, early identification of illness and provision of appropriate care and referral. [12] Post 42 days of age, interaction of infants with the health system is largely dependent on family action, centered around taking the baby for immunization and care seeking for illness. A sustained support to promote survival and growth at household level especially to those born with low birth weight is infrequent, weak and fragmented.

It is important to examine whether child health programs should provide special and more intense surveillance and support beyond 42 days for those with low birth weight. Further, should the additional surveillance and support be directed to a sub-population of LBWs or should it be provided to all low birth weights? The evidence that would compel additional follow up and support should be based on the additional risk of mortality, morbidity, stunting and cognitive deficits in the low birth weights. We believe contemporary data on the outcome of LBW infants for the neonatal and post-neonatal period are required to determine the extent to which home care program needs to be stretched. Home care programs cost resources and policy makers require local evidence from recent data on adverse outcomes including mortality rates.

With the aim of adding to the evidence base, we performed a secondary data analysis utilizing the data from an individually randomized, double masked, placebo controlled trial. The primary trial aimed at assessing the efficacy of neonatal oral supplementation with vitamin A within 72 hours of birth in reducing mortality within 6 months of infant age.[13] The study found no effect of intervention on mortality between supplementation and 6 months of

age. The underlying hypothesis of the current secondary data analysis was that LBW infants would be at a higher risk of mortality, hospitalization and sub-optimal breastfeeding practices during entire infancy, compared to those with normal birth weight (i.e. birth weight ≥2500 grams). The primary objective of the analysis was to examine the relationship between birth weight and mortality in infants born in rural Haryana, India. As a secondary objective, association of birth weight with hospitalization and breastfeeding practices was examined. This information may be helpful to improve the design and intensity of efforts for additional care directed towards low birth weight infants in the post-neonatal period.

METHODS

Study design and setting

We conducted secondary analysis on data from the Neovita trial, a large individually randomized, double-masked, placebo controlled trial of neonatal vitamin A supplementation.[13,14] This study was conducted from June 2010 till July 2012, in Faridabad and Palwal districts in the state of Haryana, North India. The primary aim of the trial was to evaluate the effect of single dose vitamin A supplementation, given within 72 hours of birth, on mortality in the first 6 months of life. The trial procedures and details of study area have been described in detail elsewhere.[13,14]

Ethical clearance

The primary trial (Neovita) was funded by World Health Organization (WHO) through a grant from Bill and Melinda Gates Foundation (BMGF). The trial was approved by the ethics review committees of World Health Organization (WHO) and Society for Applied Studies, New Delhi. Permission and approvals were taken from the state government of Haryana. The trial is registered with ClinicalTrials.gov, number NCT01138449. All the concerned investigators of the primary trial gave permission to use the data for this secondary analysis.

Enrolment and data collection

The primary trial aimed to assess the efficacy of neonatal oral vitamin A supplementation on mortality within 6 months of age. Only those infants were included in the trial that were identified within 72 hours of birth so that the intervention could be given as close to birth as possible. Pregnant women were identified through periodic household surveillance. For each live birth identified, the study team visited the family, explained the trial and screened the infant against pre-defined eligibility criteria (infant aged ≤ 72 hours at screening who could suck or feed and whose family members intended to stay in the study area for at least 6 months). Written consent was obtained from at least one parent i.e. mother or father of the eligible infant. The enrolled infant was weighed by the study team members who were trained and standardized for birth weight measurement. Re-standardization exercises were done every six months. An independent team of study supervisors did random spot checks of all workers once a month and monitored quality of performance.

At enrolment, information was collected on household characteristics (caste, religion, and socio-economic variables to ascertain wealth quintile), infant characteristics (birth weight and sex), birth related characteristics (place of delivery, multiple births, parity) and maternal characteristics (age, education and occupation). Infants were visited on the first and third day to document post supplementation adverse events and to obtain information on the time of breastfeeding initiation in hours after birth (if not already initiated at the enrolment visit) and colostrum intake.

Each enrolled infant was followed up till 12 months of age. Infants were contacted when aged 29 days and at 3, 6 and 12 months and at each visit, information was collected or ascertained on feeding practices, hospitalization since last visit and vital status. The study team member asked about what the infant was fed in the previous 24 hours from the time of visit, including

breast milk, plain water, animal milk, other fluids, medicines and solid food. A hospitalization was defined as either an inpatient admission (where an infant received an inpatient slip with a registration number and allotted a bed) or a stay of ≥ 6 hours duration in the hospital including the emergency services, diarrhoea management room or any paediatric wards of the institution.

Information on hospitalization was collected through hospital records and documents and in instances where a hospital record could not be found, information provided by the mother was considered. At the first follow up visit at 29 days, data on hospitalization was gathered since the infant was enrolled in the study. For subsequent follow up visits, information on hospitalization was collected since the last follow up visit.

Operational definitions used

Delayed initiation of breastfeeding - was defined as infant being initiated on breastfeeding after an hour of birth (>1 hour after birth).[15] This operational definition was same for infants born through normal vaginal and caesarean delivery. An additional outcome was also considered- "breastfeeding after 24 hours of birth", based on the findings of a recent review that indicated increased risk of mortality in infants who were initiated breastfeeding 24 hours after birth compared to those initiated ≤1 hour after birth.[16]

Exclusive breastfeeding- defined as infant being given no other food or drink, not even water, except breast milk (including milk expressed or from a wet nurse), with the exception of infant receiving oral rehydration salt (ORS), drops and syrups (vitamins, minerals and medicines) [15]

Outcomes for the secondary analysis

The primary outcome in our analysis was the association between birth weight and mortality during infancy. Secondary outcomes were association of birth weight with hospitalization and breastfeeding practices i.e. delayed initiation of breastfeeding, breastfeeding initiation after 24 hours of birth, non-exclusive breastfeeding at one and three months of age, and early termination of breastfeeding i.e. no breastfeeding at 6 and 12 months of age.

Data analysis

For the analysis, infants with information on birth weight, vital status, episodes of hospitalization, breastfeeding practices and data on covariates were included. Data analysis was performed using STATA version 11 (Stata Corporation, College Station, TX). The distribution of the data was examined. Proportions were calculated for categorical variables.

For analysis of mortality rates in the neonatal period, all babies enrolled in the trial were considered. For analysis of mortality between 29 to 90 days of age, 29 to 180 days and 29 to 365 days of age, only infants who were alive at 29 days of age were included in the analysis. Similarly, for analysis of hospitalization in the neonatal period, all infants enrolled in the trial for which data on hospitalization were available were considered. For analysis of hospitalization from 29 to 90 days of age, 29 to 180 days of age and 29 to 365 days of age, only infants who were alive at 29 days and had data on hospitalization within the specified time period were included in the analysis.

For delayed initiation of breastfeeding and breastfeeding after 24 hours of birth, infants were included in the analysis only if breastfeeding was initiated at any time after birth. For non-exclusive breastfeeding at 1 and 3 months, only infants alive at 1 month and 3 months of age, respectively, for whom breastfeeding data were available, were included in the analysis. Similarly, for no breastfeeding at 6 and 12 months of age, only infants that were alive at 6

and 12 months and information was available on their breastfeeding status were included in the analysis. Infants in whom breastfeeding was reported to be stopped at the time of visits at 6 and 12 months of age, irrespective of their prior breastfeeding status, were included under "no breastfeeding" category.

Log binomial model was used to assess the relationship between birth weight and mortality, hospitalization and breastfeeding practices. For small number of events, as it was for most of the outcomes assessed in this study, relative risk (RR) and odd ratio (OR) are usually comparable in magnitude and either of the two could be used. We used relative risk (RR) to express effect sizes as infants were prospectively followed up since enrolment into the study till 12 months of age. Birth weight was the exposure of interest and was categorized into ≥2500, 2000-2499 and <2000 grams. Birth weight category of <1500 grams was not considered because of a very small proportion of infants in this weight category (<1%). Adjustment was done for other covariates that were significant on univariate analysis at a p-value of <0.20[17,18] Covariates considered were: infant sex, multiple births, maternal age, maternal education, maternal education, parity, place of delivery, type of delivery, religion, caste , wealth quintile and administration of single dose of vitamin A (intervention in the primary trial). Reliable gestational age data based on ultrasound could not be obtained and therefore, analysis based on prematurity and intrauterine growth retardation could not be conducted. Assessment for effect modification (i.e. potential interaction) between birth weight and all covariates was done using an interaction term in the model. Likelihood ratio test was used to compare models with or without the interaction term. Post-hoc power calculation was also done for the outcomes related to mortality, hospitalization and breastfeeding practices at all the age ranges considered for the analysis. Population attributable risks were calculated against each birth weight category for each of the three outcomes i.e. mortality, hospitalization and breastfeeding practices across the different age

ranges. Population attributable risks were calculated using the following formula: P_{pop} * (RR-1)/[P_{pop} * (RR-1) + 1] ; where P_{pop}= proportion of exposed subjects in the study population and RR= risk ratio.[19,20]

Patient and public involvement

The current study involves secondary data analysis and therefore patients and/or public were not directly involved in the conduct of the study.

RESULTS

Characteristics of the study population

Figure 1 shows the overall flow of study participants in the primary trial. A total of 44,984 infants were recruited within 72 hours of birth, of which 65% were enrolled within 24 hours of birth. The characteristics of the population are presented in Table 1. Out of the enrolled infants, 10,658 (23.7%) weighed <2500 grams. The mean birth weight (SD) was 2732.9 (420.1) grams. Mean (SD) age of mothers was 23.9 (4.1) years. Nearly half the infants were born at home (43.3%); a third of the mothers were primiparous (32.7%) and around half of the infants were males (52.1%).

Association of birth weight with mortality during infancy

Analysis on association of birth weight with mortality outcome at all age range considered in the analysis i.e. enrolment to 28 days; 29 to 90 days; 29 to 180 days and 29 to 365 days, had a power of 100% at an alpha of 0.05. Table 2 shows the association between birth weight and mortality during the first year of life. After adjustment for covariates, being born with low birth weight, especially with a birth weight of less than 2000 gram, was associated with higher risk of mortality compared to normal birth weight infants during the whole infancy. Supplementary table 1 shows the findings of univariate analysis of covariates with mortality outcome during the neonatal and post-neonatal period. In the neonatal period, those with birth

weight between 2000-2499 grams had around 2.5 fold higher risk of death (RR 2.56; 95% CI, 2.13-3.12) while those with <2000 grams had 16 times higher risk (RR 15.64; 95% CI, 12.90-19.44). After the neonatal period, this increased risk of death in LBWs was observed between 29 to 90 days of age (RR 2.14; 95% CI, 1.74-2.58), 29 to 180 days of age (RR 2.08; 95% CI, 1.77-2.36) and 29 to 365 days of age (RR 1.92; 95% CI, 1.71-2.15). In context of mortality, the population attributable risk (PAR) for low birth weight was as high as 41% in the neonatal period and 17.6% for the post neonatal period till end of infancy. No statistically significant interaction was found between birth weight and the covariates included in the model for both neonatal and post-neonatal mortality. The interaction was specifically assessed for infant sex and was non-significant (P-value of 0.147 and 0.284 for neonatal and post-neonatal mortality respectively).

Association of birth weight with hospitalization during infancy

For risk of hospitalization in the neonatal period (i.e. enrolment to 28 days), the comparison between normal and low birth weight infants had a power of 100%. The power was lower for analysis of risk of hospitalization between 29-90 days of age (38.8%), between 29-180 days of age (41.3%) and between 29-365 days of age (46.6%). Supplementary table 2 shows the findings of univariate analysis of covariates with hospitalization as an outcome, during the neonatal and post-neonatal period. In the neonatal period, low birth weight infants were at an increased risk for hospitalization (RR 1.86; 95% CI, 1.64-2.11) compared to normal birth weight infants after adjustment for all potential covariates. This increased risk was observed in infants with birth weight between 2000 to 2499 grams (RR 1.73; 95% CI, 1.52-1.98) and was even higher among those <2000 grams (RR 3.13; 95% CI, 2.45-3.99) (Table 3). For the rest of infancy, although LBW infants remained at an increased risk of hospitalization, this risk was largely driven by infants <2000 grams. Overall, the relative risk of hospitalization between 29 to 365 days of age was 1.13 (95% CI, 1.05-1.21) in LBW infants and for those

with birth weight <2000 grams, it was 1.74 (95% CI, 1.46-2.06). The population attributable risk for hospitalization in LBWs was around 17% in the neonatal period and reduced to only 3% in post-neonatal period till 365 days of age (Table 3). No statistically significant interaction was found between birth weight and the covariates included in the model for hospitalization. For infant sex, the interaction effect was non-significant (P-value of 0.988 and 0.621 for hospitalization in the neonatal and post-neonatal period respectively)

Association of birth weight with breastfeeding practices

Overall, close to two-thirds of LBW babies (65.9%) had delayed initiation of breastfeeding i.e. after one hour of birth. Majority of LBW babies (63.7%) were not exclusive breastfed by one and even more (78.2%) by three month of age (Table 4). At 6 and 12 months, around 8% and 18% of LBW infants were not at all breastfed, respectively. Sub-optimal breastfeeding practices were significantly associated with low birth weight, especially with a birth weight of <2000 grams, after adjustment for all possible confounding variables (Table 4). Analysis on comparison of risk for delayed initiation of breastfeeding (>1 hour after birth), breastfeeding initiation after 24 hours of birth, non-exclusive breastfeeding at 1 month of age and no breast milk feeding at 6 and 12 months of age among normal and low birth weight infants had a power of >90%; however, the power was 54.6% for risk of non-exclusive breastfeeding at 3 months of age.

Supplementary table 2 shows the findings of the univariate analysis of covariates with breastfeeding outcomes. Compared to infants with normal birth weight, those with birth weight of <2500 grams had a slightly higher risk of initiating breastfeeding after 1 hour of birth (RR 1.03; 95% CI, 1.01-1.06) and a substantially higher risk of initiating after 24 hours of birth (RR 1.64; 95% CI, 1.45-1.81).

A higher risk of non-exclusive breastfeeding at one (RR 1.07; 95% CI, 1.02-1.15) and three (RR 1.08; 95% CI, 1.03-1.14) months was observed only in infants with birth weight of

<2000 grams. LBW infants were at a much higher risk of not being breastfed at all, compared to normal birth weight infants, at six months (RR 1.34; 95% CI, 1.23-1.46) and twelve months (RR 1.24; 95% CI, 1.18-1.30) of age. The risk was higher in infants with birth weight of less than 2000 grams i.e. (RR 1.49; 95% CI, 1.20-1.86) at 6 months and (RR 1.36; 95% CI, 1.18-1.56) at 12 months of age. The PAR for sub-optimal breastfeeding practices in LBW infants was around 13.3% for initiation of breastfeeding beyond 24 hours of birth; 7.2% for no breastfeeding at 6 months and 5.1% for no breastfeeding at 12 months of age. No statistically significant interaction of the covariates with birth weight was observed for any of the outcomes considered.

DISCUSSION

This secondary data analysis showed that in low birth weight infants, compared to those with normal birth weight, mortality in the neonatal as well as in the post neonatal period till 1 year of age was substantially higher. The PAR for mortality in low birth weight infants was highest in the neonatal period and declined at 12 months of age. The risk for hospitalization, reflecting severe morbidity, in both <2000 and 2000-2499 gram babies was higher compared to normal birth weight infants in the neonatal period; however, in post-neonatal period, the excess risk was seen only in <2000 gram infants. The risk of delayed initiation of breastfeeding and early termination of breastfeeding at 6 and 12 months of age was higher in the low birth weight group and the strength of association was substantially greater for those below 2000 grams. The PAR for delayed initiation of breastfeeding beyond 24 hours of birth was around 13%. An additional 7% and 5% of "continued breastfeeding" rates at 6 and 12 months respectively could be potentially achieved by focusing on promoting breastfeeding practices in low birth weight infants, beyond the neonatal period. Achieving even this much magnitude of benefit in appropriate breastfeeding practices is crucial as early initiation of

breastfeeding and continued breastfeeding during the first year of life and particularly in early infancy has been shown to be associated with improved survival and lesser morbidity.[21,22]

The findings of the study corroborate well with the previously published literature from LMICs. Katz J et al in their pooled analysis, utilising data from 20 cohorts from Asia, Africa and Latin America, documented the risk of post-neonatal mortality in preterm (RR 2.50; 95% CI, 1.48 – 4.22) and small for gestational age (RR 1.90; 95% CI, 1.32 – 2.73) infants. Their findings are similar to what we have observed in the current analysis. [7] A cohort study of LBW infants and their health outcomes in the first year of life from rural Ghana also found increased risk of mortality in LBWs in the post-neonatal period compared to normal birth weight infants. [23] Also, the risk of illness in LBW infants, compared to normal birth weight infants, declined in the post-neonatal period, similar to what the current analysis documents. [23]

In the same dataset we have also observed that LBW infants were at an increased risk of delay in receiving vaccination and being incompletely immunized by the end of infancy. Less than one-third (29.7%) of LBW infants were fully immunized by one year of age and proportion with delayed vaccination for DPT1 and DPT3 was 52% and 81% respectively. [24] In India, a little more than one-fourth of the babies are born with low birth weight.[25] The proportion of LBW varies by states and ranges from 22% to 36%.[26] Provision of quality care of small and sick babies is a priority issue in order to improve survival, growth and thrive of this vulnerable subset of infants. Health facilities have provision for care of small and sick infants and the home visitation programme until 42 days of age aims to improve neonatal survival and reduce morbidities, although achieving adequate quality and coverage for these neonatal interventions is a persistent challenge. [11,12]

An important issue is to decide whether extended support for infants through health system is needed beyond the neonatal period. An additional question of relevance is whether post

neonatal surveillance and support through continued home visitation by health care providers should be for all infants or restricted to low birth weights. Our data suggests that extended follow up and support could be for LBW infants and ideally be continued till the end of infancy owing to the high risk of mortality and sub-optimal breastfeeding practices. However in resource constrained settings, from the perspective of mortality reduction, the follow up could be at least till the first three months of life as it would provide maximum reward in terms of proportion of LBWs to be cared for (23.2%) and the corresponding reduction in mortality (PAR of 21%). The follow up for those less than 2000 grams could potentially be extended till the end of infancy as they constitute a small proportion of infants (2.5%) and corresponding reduction in mortality would be 5.6%. The extended follow up would be particularly beneficial in areas where post-neonatal mortality is high. Since wasting and stunting are also highly prevalent in India, particularly in those born with low birth weight; there is a case for extended home based surveillance and delivery of evidence based interventions to infants in most parts of the country. [27-29] The interventions could constitute monthly home visits by community health workers for growth monitoring, counselling caregivers on optimal infant care practices including recognition of illness and prompt care seeking, lactation support, promoting timely immunization, and educating caregivers on appropriate complementary feeding. Such package of interventions might be expected to improve survival, growth and development. In addition, it may lead to lower health care costs, particularly out of pocket expenses by the family, as in many parts of India care for infant illnesses is commonly sought from private practitioners. [30,31]

The current program during the neonatal period targets all neonates which is appropriate. Our findings suggest the need for increasing the duration of contacts for the LBWs. There should be focus on improving the quality of health care provider-family interactions and follow up action when merited. The current situation where immunization is the only available contact with LBW, in the post neonatal period, leaves a large proportion of LBW infants vulnerable

to premature death or poor growth and development. There is an imminent need for strengthening the existing mechanism of care and support for newborns in the first 42 days of life along with introducing additional care for LBW infants through a dedicated home based programme throughout the first year of life. Availability of Accredited Social Health Activist (ASHA) who works closer to home gives a unique opportunity to design a programme linking facility to home. [32]

An informed decision whether to focus on all infants must take into account the population attributable risk (PAR) for other adverse outcomes such as stunting. Overall, in areas of high mortality during infancy and high stunting rates, a case can be made for extended home contacts for infants beyond the neonatal period. Whether the cost-benefits may be greater and the feasibility increased by focusing such programs on LBW infants are important aspects to consider.

Strength and limitations

The findings of current analysis have adequate generalizability as the social, economic, and demographic features of the study setting are fairly representative of large parts of Southeast Asia. The strengths of the study include robust population based surveillance system, low loss to follow up and large sample size. Also, for each of the outcomes considered in the analysis, data were available for >98% of the infants, reducing the risk of selection bias. All the infants were recruited within 72 hours of birth and their weight was measured by trained study team, thereby reducing chances of misclassification of infants by birth weight. In order to achieve adequate quality of data, the study team members were rigorously trained and underwent periodic inter and intra observer standardization exercises.

A limitation that must be considered while interpreting the findings is that the main trial did not include babies who were unable to feed in the first 72 hours of birth. This was because

the trial aimed at supplementing newborns orally with vitamin A within 72 hours of birth and assess it effect on mortality within 6 months of infant age. To assess whether infants who were not enrolled in the study (i.e. those who died before contact for screening, those who could not be enrolled because of serious illness, or those who were admitted in intensive care) were of low birth weight, attempt was made to obtain birth weights for all infants who were screened but not enrolled. Weights were obtained by study workers at the visit to assess eligibility for screening. Out of the 2793 infants excluded, weights for 2087 was obtained and of these infants, 748 (36%) were low birth weight. In such babies, inadequate breastfeeding practices, morbidity and mortality would probably have been higher. Excluding them, therefore, may have made our estimates more conservative. The risk of mortality, hospitalization and sub-optimal breastfeeding practices might have been more than what we found, had such LBW babies were included in the analysis. There are some other limitations inherent to the secondary data analysis. In the primary trial, reliable data on gestational age was not obtained, making it impossible to assess, in the current analysis, how the outcomes might have been influenced by prematurity. Further, for some of the outcomes such as non-exclusive breastfeeding at 3 months of age, hospitalization between 29-90 days of age, 29-180 days of age and 29-365 days of age, the power was around 50%.

Conclusion

Low birth weight infants experience high risk of mortality, hospitalization and sub-optimal breastfeeding practices even beyond the neonatal period and therefore require continued care and support through health system in order to promote their survival. The current mechanism of home visitation program in India that focuses on the first 42 days of life may need to be extended to at least cover the first three months of infancy and if resources permit, till end of infancy.

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Data sharing statement: No additional data available. Request for data used in the current analysis can be directed to the corresponding author.

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Table 1. Baseline characteristics of infants randomized in the primary trial (N=44,984)

Variables	n (%)
HOUSEHOLD CHARACTERISTICS	
Religion	
Hindu	34573 (76.9)
Muslim	9906 (22.0)
Others¶	505 (1.1)
Caste **	
General	12041 (26.8)
Other Backward Class (OBC)	21892 (48.7)
Scheduled Caste/Tribe (SC/ST)	11051 (24.5)
MATERNAL CHARACTERISTICS	
Mother's age (in years)	
<20	3563 (8.0)
20-30	38747 (86.1)
>30	2674 (5.9)
Mother's education (Years of schooling)	
Illiterate (0)	18814 (41.8)
1 to ≤9	16667 (37.1)
10 to <12	4383 (9.7)
≥12	5120 (11.4)
Mother's working status	
Work outside home	1142 (2.5)
Home maker	43842 (97.5)
BIRTH RELATED CHARACTERISTICS	
Place of delivery*	
Home	19478 (43.3)
Government facility	14136 (31.4)
Private facility	11326 (25.2)
Type of delivery	
Normal	42210 (93.8)
Caesarean	2592 (5.8)
Assisted	182 (0.4)
Singleton	44413 (98.7)
Multiple	571 (1.3)
Parity	
Multiparity	30257 (67.3)
Primiparity	14727 (32.7)
INFANT CHARACTERISTICS	
Sex of the baby	
Male	23418 (52.1)
Female	21566 (47.9)
Birth weight (in grams)†	
≥2500	34317 (76.3)
2000-2499	9403 (20.9)
<2000	1255 (2.8)

¶ others- Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist; **General- group that do not qualify for any of the positive discrimination schemes by Government of India (GOI), OBC- term used by the Government of India to classify castes which are socially and educationally disadvantaged, SC/ST- official designations given to groups of historically disadvantaged indigenous people in India; *remaining 44 births took place on way to health facility; † 9 infants had data missing on birth weight

Table 2. Association of mortality rates in the first year of life by birth weight in infants from rural Haryana, North India

	Number of deaths (rate per 1000 live births	Number of infants**	Univariate	Multivariate§	PAR (%)
			RR (95% CI)	RR (95% CI)	
Neonatal mortality (from enrolment to 28 days)					
Total number	---	44975			
Birth weight (grams)					
>=2500	244 (7.1)	34,317 (76.3)	Ref	Ref	-----
<2500	335 (31.4)	10658 (23.7)	4.42 (3.78-5.23)	3.92 (3.33-4.66)	41
2000-2499	181 (19.2)	9403 (20.9)	2.71 (2.27-3.31)	2.56 (2.13-3.12)*	24.6
<2000	154 (122.7)	1255 (2.8)	17.28 (14.22-20.89)	15.64 (12.90-19.44)*	29.1
Post Neonatal mortality (29-90 days)					
Total number	----	44396			
Birth weight (grams)					
>=2500	249 (7.3)	34073 (76.8)	Ref	Ref	-----
<2500	203 (19.7)	10323 (23.2)	2.69 (2.21-3.19)	2.14 (1.74-2.58)	21
2000-2499	126 (13.7)	9222 (20.7)	1.88 (1.51-2.33)	1.68 (1.36-2.08)*	12.3
<2000	77 (69.9)	1101 (2.5)	9.57 (7.32-12.07)	6.43 (4.69-8.34)*	11.9
Post Neonatal mortality (29-180 days)					
Total number	----	44396			
Birth weight (grams)					
>=2500	453 (13.3)	34073 (76.8)	Ref	Ref	-----
<2500	350 (33.9)	10323 (23.2)	2.55 (2.21-2.93)	2.08 (1.77-2.36)	20
2000-2499	249(27.0)	9222 (20.7)	2.01 (1.72-2.34)	1.78 (1.52-2.09)*	13.9
<2000	101 (91.7)	1101 (2.5)	6.89 (5.47-8.36)	4.24 (3.28-5.37)*	7.5
Post Neonatal mortality (29 to 365 days)					
Total number	---	44396			
Birth weight (grams)					
>=2500	725 (21.3)	34073 (76.8)	Ref	Ref	---
<2500	514 (49.8)	10323 (23.2)	2.33 (2.07-2.58)	1.92 (1.71-2.15)	17.6
2000-2499	392 (42.5)	9222 (20.7)	1.99 (1.76-2.24)	1.76 (1.54-1.99)	13.6
<2000	122 (110.8)	1101 (2.5)	5.20 (4.34-6.16)	3.38 (2.71-4.12)	5.6

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, caste , wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial); ** 9 infants had data missing on birth weight; *statistical significance at p-value<0.05; PAR- population attributable risk

Table 3. Association of hospitalization for severe morbidity in the first year of life, by birth weight in infants from rural Haryana, North India

	Infants with ≥1 episode (s) of hospitalization (%)	Number of infants**	Univariate	Multivariate§	PAR (%)
			Unadjusted RR (95% CI)	Adjusted RR (95% CI)	
Hospitalization from enrolment to 28 days					
Total number	---	44481			
Birth weight (grams)					
>=2500	724 (2.13)	34028 (76.5)	Ref	Ref	-----
<2500	383 (3.66)	10453 (23.5)	1.72 (1.51-1.93)	1.86 (1.64-2.11)*	16.8
2000-2499	311 (3.35)	9273 (20.8)	1.57 (1.37-1.78)	1.73 (1.52-1.98)*	13.2
<2000	72 (6.10)	1180 (2.7)	2.89 (2.27-3.63)	3.13 (2.45-3.99)*	5.4
Hospitalization in post neonatal period (29-90 days)					
Total number	---	43820			
Birth weight (grams)					
>=2500	582(1.73)	33674 (76.8)	Ref	Ref	-----
<2500	201 (1.98)	10146 (23.2)	1.15 (0.98-1.35)	1.20 (1.02-1.42)*	4.4
2000-2499	161(1.78)	9076 (20.7)	1.03 (0.87-1.22)	1.11 (0.93-1.33)	2.2
<2000	40 (3.74)	1070 (2.5)	2.17 (1.58-2.97)	2.11 (1.50-2.95)*	2.6
Hospitalization in post neonatal period (29-180 days)					
Total number	---	43056			
Birth weight (grams)					
>=2500	1444 (4.35)	33198 (77.1)	Ref	Ref	---
<2500	469 (4.76)	9860 (22.9)	1.09 (0.98-1.21)	1.15 (1.03-1.27)*	3.3
2000-2499	376 (4.24)	8863 (20.6)	0.97 (0.87-1.09)	1.05 (0.94-1.18)	1.0
<2000	93 (9.33)	997 (2.3)	2.14 (1.76-2.62)	2.08 (1.69-2.59)*	2.4
Hospitalization in post neonatal period (29 to 365 days)					
Total number	---	42708			
Birth weight (grams)					
>=2500	3046 (9.23)	32966 (77.2)	Ref	Ref	---
<2500	960 (9.86)	9742 (22.8)	1.07 (1.00-1.14)	1.13 (1.05-1.21)*	2.9
2000-2499	803 (9.17)	8761 (20.5)	0.99 (0.92-1.07)	1.07 (0.98-1.15)	1.4
<2000	157 (16.0)	981 (2.3)	1.73 (1.49-2.01)	1.74 (1.46-2.06)*	1.7

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, caste , wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial), *statistical significance at p-value<0.05; **Denotes the number of infants that were alive at the start point of analysis time frame and had data on hospitalization during the period under

consideration e.g. for analysis of hospitalization between 1 to 6 months of age, only those infants were included in analysis that were alive at 1 month of age and had data on hospitalization between 1 to 6 months of age; PAR- population attributable risk

Table 4 . Association of breastfeeding practices by birth weight in infants from rural Haryana, North India

	Number of infants with outcome of interest (%)	Total no. of infants**	Univariable	Multivariable§	PAR (%)
			RR (95% CI)	RR (95% CI)	
Delayed initiation of breastfeeding (BF initiated after 1 hour of birth)					
Total number	---	40878			
Birth weight (grams)					
>=2500	19906 (64.0)	31090 (76.1)	Ref	Ref	-----
<2500	6457 (65.9)	9788 (23.9)	1.03 (1.01-1.05)	1.03 (1.01-1.06)*	0.71
2000-2499	5685 (65.7)	8654 (21.2)	1.03 (1.01-1.05)	1.04 (1.01-1.06)*	0.84
<2000	772 (68.1)	1134 (2.7)	1.06 (1.02-1.11)	1.07 (1.03-1.15)*	0.19
Breastfeeding after 24 hours of birth					
Total number	----	40878			
Birth weight (grams)					
>=2500	1002 (3.2)	31090 (76.1)	Ref	Ref	-----
<2500	497 (5.1)	9788 (23.9)	1.59 (1.41-1.74)	1.64 (1.45-1.81)*	13.3
2000-2499	413 (4.8)	8654 (21.2)	1.49 (1.32-1.65)	1.55 (1.37-1.73)*	10.4
<2000	84 (7.4)	1134 (2.7)	2.31 (1.85-2.84)	2.43 (1.91-3.07)*	3.7
Non-exclusive breastfeeding at 1 month					
Total number	----	43656			
Birth weight (grams)					
>=2500	20491 (61.1)	33541 (76.8)	Ref	Ref	-----
<2500	6446 (63.7)	10115 (23.2)	1.04 (1.03-1.07)	1.03 (0.99-1.05)	0.69
2000-2499	5709(63.1)	9042 (20.7)	1.03 (1.02-1.05)	1.02 (0.98-1.05)	0.41
<2000	737 (68.7)	1073 (2.5)	1.12 (1.08-1.17)	1.07 (1.02-1.15)*	0.17
Non-exclusive breastfeeding at 3 month					
Total number	---	42628			
Birth weight (grams)					
>=2500	25401 (77.2)	32877 (77.1)	Ref	Ref	---
<2500	7630 (78.2)	9751 (22.9)	1.01 (1.00-1.03)	1.01 (0.98-1.03)	0.22
2000-2499	6793 (77.5)	8759 (20.6)	1.00 (0.98-1.02)	1.02 (0.97-1.06)	0.41
<2000	837 (84.4)	992 (2.3)	1.09 (1.07-1.13)	1.08 (1.03-1.14)*	0.19

No breastfeeding at 6 months					
Total number	---	42392			
Birth weight (grams)					
>=2500	1936 (5.91)	32744 (77.2)	Ref	Ref	---
<2500	778 (8.06)	9648 (22.8)	1.36 (1.26-1.49)	1.34 (1.23-1.46)*	7.2
2000-2499	682 (7.86)	8676 (20.5)	1.33 (1.22-1.45)	1.32 (1.21-1.45)*	6.1
<2000	96 (9.87)	972 (2.3)	1.67 (1.37-2.03)	1.49 (1.20-1.86)*	1.1
No breastfeeding at 12 months					
Total number	---	42492			
Birth weight (grams)					
>=2500	4776 (14.5)	32883 (77.4)	Ref	Ref	----
<2500	1791 (18.6)	9609 (22.6)	1.28 (1.22-1.35)	1.24 (1.18-1.30)*	5.1
2000-2499	1572 (18.2)	8642 (20.3)	1.26 (1.19-1.32)	1.23 (1.16-1.30)*	4.5
<2000	219 (22.7)	967 (2.3)	1.57 (1.37-1.78)	1.36 (1.18-1.56)*	0.8

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, caste , wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial); *statistical significance at p-value<0.05; **Denotes the total number of infants for which desired breastfeeding information was available; PAR-population attributable risk

Figure 1 . Overall flow of infants recruited in the primary trial

*LBW- Low birth Weight; NBW- Normal birth weight; 9 infants had data missing on birth weight

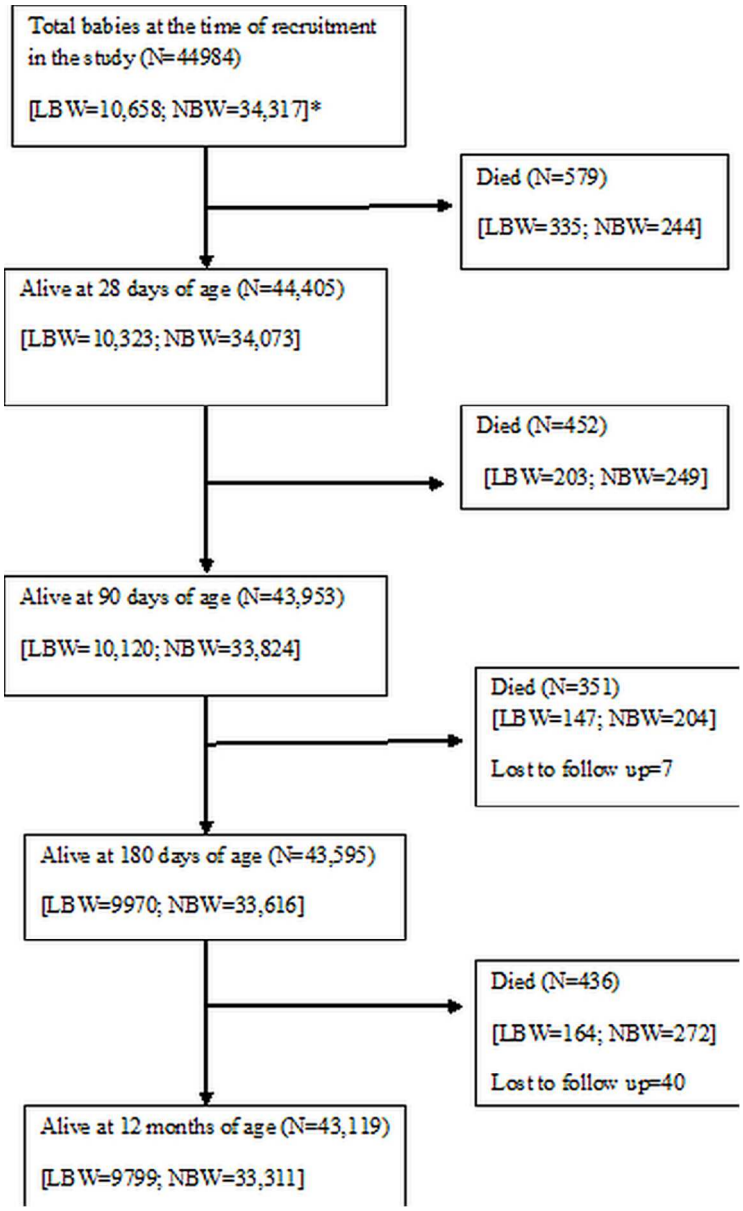

Figure 1 . Overall flow of infants recruited in the primary trial

Supplementary Table 1. Findings of the univariate analysis of covariates with the outcomes related to mortality and hospitalization

	Univariate analysis Crude RR (95% Confidence Intervals); P-value			
	Neonatal mortality (from enrolment to 28 days)	**Post Neonatal mortality (29-365 days)**	**Neonatal hospitalization (from enrolment to 28 days)**	**Post Neonatal hospitalization (29 to 365 days)**
Place of delivery				
Home	Ref	Ref	Ref	Ref
Government facility	0.66 (0.54, 0.80); <0.001	0.80 (0.71, 0.91); 0.001	1.17 (1.00, 1.35); 0.051	1.20 (1.12, 1.29); <0.001
Private facility	0.71 (0.58, 0.87); 0.001	0.69 (0.59, 0.79); <0.001	1.96 (1.71, 2.25); <0.001	1.61 (1.50, 1.73); <0.001
Type of delivery				
Normal	Ref	Ref	Ref	Ref
Assisted	--	0.77 (0.29, 2.05); 0.61	0.89 (0.34, 2.36); 0.82	1.00 (0.63, 1.60); 0.990
Caesarean	0.48 (0.29, 0.78); 0.003	0.63 (0.47, 0.84); 0.002	1.18 (0.94, 1.49); 0.14	1.34 (1.20, 1.49); <0.001
Multiple births				
No (singleton pregnancy)	Ref	Ref	Ref	Ref
Yes	4.31 (3.03, 6.13); <0.001	5.65 (4.58, 6.98); <0.001	2.56 (1.85, 3.56); <0.001	2.12 (1.76, 2.56); <0.001
Mother's age (yrs)				
<20	Ref	Ref	Ref	Ref
20-30	0.86 (0.65, 1.14); 0.309	0.81 (0.67, 0.97); 0.030	0.82 (0.67, 0.99); 0.044	1.13 (1.00, 1.26); 0.043
>30	1.28 (0.87, 1.78); 0.187	1.55 (1.21, 1.98); <0.001	0.52 (0.36, 0.74); <0.001	0.93 (0.78, 1.10); 0.384
Mother's education (Years of schooling)				
Illiterate (0)	Ref	Ref	Ref	Ref
1 to ≤9	0.72 (0.63, 0.89); 0.002	0.61 (0.54, 0.68); <0.001	1.57 (1.36, 1.81); <0.001	1.43 (1.33, 1.53); <0.001
10 to <12	0.47 (0.33, 0.68); <0.001	0.41 (0.32, 0.53); <0.001	2.26 (1.87, 2.73); <0.001	1.82 (1.65, 1.99); <0.001
≥12	0.43 (0.31, 0.61); <0.001	0.24 (0.18, 0.32); <0.001	2.59 (2.18, 3.08); <0.001	1.77 (1.62, 1.94); <0.001
Mother's working status				
Work outside home	Ref	Ref	Ref	Ref
Home maker	1.37 (0.76, 2.48); 0.300	0.86 (0.62, 1.19); 0.380	1.04 (0.71, 1.52); 0.831	0.98 (0.81, 1.18); 0.824
Religion				
Hindu	Ref	Ref	Ref	Ref

Muslim	1.20 (1.00, 1.45); 0.049	1.61 (1.43, 1.81); <0.001	0.38 (0.32, 0.47); <0.001	0.59 (0.54, 0.64); <0.001
Others	1.42 (0.74, 2.74); 0.287	0.99 (0.56, 1.74); 0.976	0.42 (0.19, 0.93); 0.031	0.75 (0.55, 1.03); 0.073
Caste				
General	Ref	Ref	Ref	Ref
Other Backward Class (OBC)	1.48 (1.20, 1.83); <0.001	1.66 (1.43, 1.94); <0.001	0.51 (0.44, 0.58); <0.001	0.76 (0.63, 0.72); <0.001
Scheduled Caste/Tribe (SC/ST)	1.42 (1.12, 1.80); 0.004	1.77 (1.49, 2.09); <0.001	0.60 (0.52, 0.70); <0.001	0.86 (0.80, 0.93); <0.001
Wealth quintile				
1 (Least poor)	Ref	Ref	Ref	Ref
2	1.53 (1.09, 2.13); 0.012	1.65 (1.29, 2.10); <0.001	0.84 (0.71, 0.97); 0.021	0.90 (0.83, 0.98); 0.013
3	2.39 (1.76, 3.25); <0.001	2.15 (1.70, 2.71); <0.001	0.59 (0.49, 0.70); <0.001	0.78 (0.72, 0.85); <0.001
4	2.74 (2.03, 3.70); <0.001	3.08 (2.46, 3.83); <0.001	0.54 (0.45, 0.64); <0.001	0.63 (0.58, 0.69); <0.001
5 (Poorest)	2.70 (1.99, 3.66); <0.001	4.17 (3.36, 5.16); <0.001	0.34 (0.28, 0.42); <0.001	0.49 (0.44, 0.54); <0.001
Parity				
Multiparity	Ref	Ref	Ref	Ref
Primiparity	1.14 (0.93, 1.42); 0.124	0.61 (0.53, 0.69); <0.001	1.76 (1.57, 1.98); <0.001	1.19 (1.13, 1.27); <0.001
Infant sex				
Male	Ref	Ref	Ref	Ref
Female	1.36 (1.16, 1.59); <0.001	1.56 (1.39, 1.74); <0.001	0.43 (0.37, 0.49); <0.001	0.54 (0.51, 0.58); <0.001

Supplementary Table 2. Findings of the univariate analysis of covariates with the outcomes related to breastfeeding practices

	Univariate analysis Crude RR (95% Confidence Intervals); P-value			
	Delayed initiation of breastfeeding (BF initiated after 1 hour of birth)	**BF initiated after 24 hours of birth**	**No exclusive BF at 6 months**	**No breastfeeding at 12 months**
Place of delivery				
Home	Ref	Ref	Ref	Ref
Government facility	0.88 (0.87, 0.90); <0.001	0.53 (0.46, 0.62); <0.001	0.98 (0.97, 1.00); 0.03	1.08 (1.02, 1.14); 0.005
Private facility	1.22 (1.21, 1.24); <0.001	2.17 (1.95; 2.42); <0.001	0.98 (0.97, 0.99); 0.0	1.37 (1.31, 1.45); <0.001
Type of delivery				
Normal	Ref	Ref	Ref	Ref
Assisted	1.18 (0.98, 1.40); 0.073	2.25 (1.24, 4.07); 0.008	1.05 (0.98, 1.13); 0.15	1.03 (0.73, 1.46); 0.866
Caesarean	1.40 (1.32, 1.48); <0.001	7.92 (7.01, 8.95); <0.001	1.02 (1.00, 1.05); 0.03	1.24 (1.14, 1.35); <0.001
Multiple births				
No (singleton pregnancy)	Ref	Ref	Ref	Ref
Yes	1.11 (1.05, 1.18); <0.001	2.14 (1.57, 2.93); <0.001	1.18 (1.15, 1.21); <0.001	2.39 (2.11, 2.71); <0.001
Mother's age (yrs)				
<20	Ref	Ref	Ref	Ref
20-30	0.98 (0.96, 1.01); 0.251	1.01 (0.84, 1.22); 0.882	0.95 (0.94, 0.97); <0.001	0.82 (0.76, 0.88); <0.001
>30	1.09 (1.06, 1.14); <0.001	1.51 (1.18, 1.93); 0.001	0.99 (0.96, 1.01); 0.336	0.58 (0.51, 0.68); <0.001
Mother's education (Years of schooling)				
Illiterate (0)	Ref	Ref	Ref	Ref
1 to ≤9	0.93 (0.92, 0.95); <0.001	0.72 (0.64, 0.80); <0.001	0.98 (0.96, 1.01); 0.24	1.24 (1.18, 1.32); <0.001
10 to <12	0.96 (0.93, 0.98); 0.001	0.93 (0.78, 1.10); 0.398	0.94 (0.91, 0.98); 0.003	1.46 (1.34, 1.58); <0.001
≥12	1.03 (1.00, 1.05); 0.029	1.01 (0.86, 1.18); 0.903	0.95 (0.92, 0.99); 0.01	1.50 (1.39, 1.62); <0.001
Mother's working status				
Work outside home	Ref	Ref	Ref	Ref
Home maker	0.99 (0.95, 1.05); 0.955	0.84 (0.63, 1.12); 0.239	1.03 (0.82, 1.17); 0.65	0.94 (0.82, 1.08); 0.391
Religion				
Hindu	Ref	Ref	Ref	Ref
Muslim	1.28 (1.27, 1.30); <0.001	2.08 (1.88, 2.31); <0.001	1.06 (1.05, 1.08); <0.001	0.77 (0.73, 0.82); <0.001

Others	0.92(0.84, 0.99); 0.039	0.91 (0.52, 1.59); 0.731	0.85 (0.79, 0.91); <0.001	0.98 (0.80, 1.21); 0.883
Caste				
General	Ref	Ref	Ref	Ref
Other Backward Class (OBC)	1.09 (1.08, 1.12); <0.001	1.08 (0.96, 1.20); 0.211	1.05 (1.04, 1.06); <0.001	0.77 (0.73, 0.81); <0.001
Scheduled Caste/Tribe (SC/ST)	0.93 (0.91, 0.95); <0.001	0.53 (0.45, 0.62); <0.001	1.03 (1.01, 1.05); <0.001	0.84 (0.79, 0.88); <0.001
Wealth quintile				
1 (Least poor)	Ref	Ref	Ref	Ref
2	0.93 (0.91, 0.95); <0.001	0.72 (0.62, 0.85);<0.001	1.04 (1.02, 1.06); <0.001	0.94 (0.88, 0.99); 0.034
3	0.92 (0.90, 0.95); <0.001	0.73 (0.62, 0.85); <0.001	1.02 (1.00, 1.04); 0.031	0.78 (0.73, 0.84); <0.001
4	0.93 (0.91, 0.96); <0.001	0.72 (0.61, 0.84); <0.001	1.02 (1.00, 1.03); 0.071	0.71 (0.66, 0.76); <0.001
5 (Poorest)	0.99 (0.96, 1.01); 0.188	0.95 (0.82, 1.09); 0.478	1.03 (1.01, 1.04); 0.001	0.55 (0.51, 0.58); <0.001
Parity				
Multiparity	Ref	Ref	Ref	Ref
Primiparity	1.05 (1.04, 1.07); <0.001	1.32 (1.19, 1.46); <0.001	1.05 (1.04, 1.06); <0.001	1.40 (1.34, 1.47); <0.001
Infant sex				
Male	Ref	Ref	Ref	Ref
Female	1.03 (1.01, 1.04); <0.001	0.84(0.76, 0.93); 0.001	0.99 (0.98, 1.00); 0.071	1.13 (1.08, 1.18); <0.001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page no. in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes (Page -3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes (Page -3)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes (Page 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes (Page 5)
Methods			
Study design	4	Present key elements of study design early in the paper	Yes (Page 5-9)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes (Page 5-9)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes (Page 5-9)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Yes (Page 10,21,23-26)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes (Page 5-9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes (Page 5-9)
Bias	9	Describe any efforts to address potential sources of bias	Yes (Page 5-9)
Study size	10	Explain how the study size was arrived at	Yes (Page 5-9)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes (Page 5-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes (Page 5-9)
		(*b*) Describe any methods used to examine subgroups and interactions	Yes (Page 5-9)
		(*c*) Explain how missing data were addressed	Yes (Page 5-9)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Yes (Page 5-9)
		(*e*) Describe any sensitivity analyses	We did a sub group analysis by sub-categories of low birth weight

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes (Page 20)
		(b) Give reasons for non-participation at each stage	Yes (page 10-12; page 20)
		(c) Consider use of a flow diagram	Yes (Page 20)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest	Yes (Page 23-26)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Yes (Page 23-26)
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes (Page 10-12; 23-26)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes (Page 10-12; 23-26)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes (Page 10-12; 23-26)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes (Page 10-12; 23-26)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes (Page 12-16)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes (Page 12-16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes (Page 12-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes (Page 12-16)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes (Page 1)

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Risk of post-neonatal mortality, hospitalization and sub-optimal breastfeeding practices in low birth weight infants from rural Haryana, India: Findings from a secondary data analysis

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TITLE PAGE

Risk of post-neonatal mortality, hospitalization and sub-optimal breastfeeding practices in low birth weight infants from rural Haryana, India: Findings from a secondary data analysis

Ravi Prakash Upadhyay, MD [1], Jose Martines, PhD [2], Sunita Taneja PhD [1], Sarmila Mazumder PhD [1], Rajiv Bahl PhD[3] ,Nita Bhandari PhD[1], Suresh Dalpath MPH[4], Maharaj Kishan Bhan, MD [5,6]

1. Centre for Health Research and Development, Society for Applied Studies, New Delhi
2. Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway
3. Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland
4. National Health Mission, Haryana
5. Indian Institute of Technology (IIT), New Delhi, India
6. Knowledge Integration and Translational Platform (KnIT), Biotechnology Industry Research Assistance Council (BIRAC), New Delhi, India

Corresponding author: Dr. Ravi Prakash Upadhyay, Research Scientist, Center for Health Research and Development, Society for Applied Studies, Kalu Sarai, New Delhi, Pin-110016

E-mail: ravi.upadhyay@sas.org.in

Phone number: +911146043751

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Clinical Trial registry name and registration number: The trial is registered with ClinicalTrials.gov, number NCT01138449.

Data sharing statement: No additional data available. Request for data used in the current analysis can be directed to the corresponding author.

Abbreviations

LBW- Low Birth Weight

LMICs- Low and Middle Income Countries

NBCC- Newborn Care Corner

NBSU- Newborn Stabilization Unit

SNCU- Special Newborn Care Unit

WHO- World Health Organization

ORS- Oral Rehydration Salt

RR- Risk Ratio

PAR- Population Attributable Risk

ASHA- Accredited Social Health Activist

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Contributor's statement page

RPU conceptualized the study, did the formal analysis, drafted the manuscript
JM conceptualized the study, helped in analysis and preparation of the manuscript
RB conceptualized the study, helped in the formal analysis and reviewed and revised the manuscript
ST, SM, NB and SD provided overall coordination and supervised data procurement; provided inputs in the analysis, manuscript writing and critically reviewed the manuscript
MKB conceptualized the study, helped in framing the plan of analysis and provided critical feedback throughout the analysis and manuscript preparation

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: Low birth weight (LBW) is a risk factor for neonatal mortality and morbidity. It is important to examine whether this risk persists beyond neonatal period. The current secondary data analysis aimed to examine association of birth weight with mortality, hospitalization and breast feeding practices during infancy.

Design: Data from a large randomized controlled trial of neonatal vitamin A supplementation (Neovita) trial were used. Log binomial model was applied to assess association between birth weight and mortality, hospitalization and breastfeeding practices.

Setting: Rural Haryana, North India

Participants: Newborns recruited in the primary intervention trial that aimed to evaluate the effect of single dose oral vitamin A supplementation on mortality in the first 6 months of life.

Results: We recruited a total of 44,984 infants, of which 10,658 (23.7%) were born LBW i.e. birth weight less than 2500 grams. In the neonatal period, LBW babies had 4 times higher risk of mortality (RR 3.92; 95% CI, 3.33-4.66) compared with normal birth weight babies. In the post-neonatal period, the risk was two times higher (RR 1.92; 95% CI, 1.71-2.15); even higher in those with birth weight <2000 grams (RR 3.38; 95% CI, 2.71-4.12). The risk of hospitalization in the neonatal period and post-neonatal period was (RR 1.86; 95% CI, 1.64-2.11) and (RR 1.13; 95% CI, 1.05-1.21) respectively. LBWs were at increased risk of breastfeeding initiation 24 hours after birth (RR 1.64; 95% CI, 1.45-1.81), no breastfeeding at 6 months (RR 1.34; 95% CI, 1.23-1.46) and at 12 months of age (RR 1.24; 95% CI, 1.18-1.30).

Conclusions: LBW babies, especially those with birth weight of <2000 grams, were at increased risk of mortality, hospitalization and sub-optimal breastfeeding practices during entire infancy and therefore require additional care beyond the first 28 days of life.

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Key words: Low birth weight; infant mortality; post-neonatal mortality; hospitalization risk; breastfeeding practices; extended home visitation; care and support; India

Strengths and limitations of the study

- Robust population based surveillance system, low loss to follow up and large sample size.
- Birth weight measured by trained study team, thereby reducing chances of misclassification
- Findings are generalizable to large parts of Southeast Asia because of similar social, economic, and demographic features.
- Main trial did not include babies who either died or were unable to feed in the first 72 hours of birth; 36% of which were low birth weight. Excluding them in the primary trial may have made the estimates, especially for mortality, more conservative.
- Lack of reliable data on gestational age restricted analysis by prematurity and intrauterine growth retardation

INTRODUCTION

Approximately 15% of infants in low and middle income countries (LMICs) are born low birth weight (LBW) (i.e. birth weight <2500 grams). [1] In 2010, in LMICs, an estimated 18 million infants were born with low birth weight, of which around 7.5 million babies (41%) were born in India alone.[1] LBW infants face high risk of poor health outcomes such as growth retardation, developmental delay and death.[2-5] Recent studies on mortality risk by gestational age in LMICs document high risk of neonatal as well as post-neonatal mortality in preterms and small for gestational age infants.[6,7] Existing programs for infant care, globally as well as in India, are heavily investing in improving facility based care for small and sick infants alongside efforts to increase institutional deliveries so that quality care, without delay, could be provided to "at-risk" newborns. In India, with the introduction of government schemes such as Janani Suraksha Yojna (JSK) and Janani Shishu Suraksha Karyakaram (JSSK), a substantial increase in institutional deliveries has occurred.[8,9] According to the recent National Family Health Survey (NFHS-4), the institutional delivery rate for India is 79%.[10] Janani Suraksha Yojana (JSY), a conditional cash transfer scheme was introduced in the year 2005, with a strategy to link cash assistance to institutional delivery.[8,9] Due to JSY, institutional deliveries across the country increased but with a few limitations such as high out of pocket expenditure by families especially for purchase of the drugs and transport. In the view of these limitations, Government of India introduced Janani Shishu Suraksha Karyakram (JSSK) scheme in June 2011.[9] Under this scheme- birth of the baby through normal vaginal delivery, caesarean section, drugs and consumables, diagnostics and transport between home and health facility is provided free of cost.[9]

Newborn care facilities have been established at various levels of Indian public health system. These include newborn care corners (NBCCs) to provide immediate care after childbirth; newborn stabilization units (NBSUs) at community health centers/first referral

units for management of selected conditions and to stabilize sick newborns before referral to higher centres; and Special Newborn Care Units (SNCUs) at district/sub-district hospitals to care for sick newborns. [11] Post-discharge from the birth facility, all newborns are to be visited by a community health worker; a total of 6 visits within 42 days of age. These visits aim to promote essential newborn care practices, early detection and special care of preterm and low birth weight infants, early identification of illness and provision of appropriate care and referral. [12] Post 42 days of age, interaction of infants with the health system is largely dependent on family action, centered around taking the baby for immunization and care seeking for illness. A sustained support to promote survival and growth at household level especially to those born with low birth weight is infrequent, weak and fragmented.

It is important to examine whether child health programs should provide special and more intense surveillance and support beyond 42 days for those with low birth weight. Further, should the additional surveillance and support be directed to a sub-population of LBWs or should it be provided to all low birth weights? The evidence that would compel additional follow up and support should be based on the additional risk of mortality, morbidity, stunting and cognitive deficits in the low birth weights. We believe contemporary data on the outcome of LBW infants for the neonatal and post-neonatal period are required to determine the extent to which home care program needs to be stretched. Home care programs cost resources and policy makers require local evidence from recent data on adverse outcomes including mortality rates.

With the aim of adding to the evidence base, we performed a secondary data analysis utilizing the data from an individually randomized, double masked, placebo controlled trial. The primary trial aimed at assessing the efficacy of neonatal oral supplementation with vitamin A within 72 hours of birth in reducing mortality within 6 months of infant age.[13] The study found no effect of intervention on mortality between supplementation and 6 months of

age. The underlying hypothesis of the current secondary data analysis was that LBW infants would be at a higher risk of mortality, hospitalization and sub-optimal breastfeeding practices during entire infancy, compared to those with normal birth weight (i.e. birth weight ≥2500 grams). The primary objective of the analysis was to examine the relationship between birth weight and mortality in infants born in rural Haryana, India. As a secondary objective, association of birth weight with hospitalization and breastfeeding practices was examined. This information may be helpful to improve the design and intensity of efforts for additional care directed towards low birth weight infants in the post-neonatal period.

METHODS

Study design and setting

We conducted secondary analysis on data from the Neovita trial, a large individually randomized, double-masked, placebo controlled trial of neonatal vitamin A supplementation.[13,14] This study was conducted from June 2010 till July 2012, in Faridabad and Palwal districts in the state of Haryana, North India. The primary aim of the trial was to evaluate the effect of single dose vitamin A supplementation, given within 72 hours of birth, on mortality in the first 6 months of life. The trial procedures and details of study area have been described in detail elsewhere.[13,14]

Ethical clearance

The primary trial (Neovita) was funded by World Health Organization (WHO) through a grant from Bill and Melinda Gates Foundation (BMGF). The trial was approved by the ethics review committees of World Health Organization (WHO) and Society for Applied Studies, New Delhi. Permission and approvals were taken from the state government of Haryana. The trial is registered with ClinicalTrials.gov, number NCT01138449. All the concerned investigators of the primary trial gave permission to use the data for this secondary analysis.

Enrolment and data collection

The primary trial aimed to assess the efficacy of neonatal oral vitamin A supplementation on mortality within 6 months of age. Only those infants were included in the trial that were identified within 72 hours of birth so that the intervention could be given as close to birth as possible. Pregnant women were identified through periodic household surveillance. For each live birth identified, the study team visited the family, explained the trial and screened the infant against pre-defined eligibility criteria (infant aged ≤ 72 hours at screening who could suck or feed and whose family members intended to stay in the study area for at least 6 months). Written consent was obtained from at least one parent i.e. mother or father of the eligible infant. The enrolled infant was weighed by the study team members who were trained and standardized for birth weight measurement. Re-standardization exercises were done every six months. An independent team of study supervisors did random spot checks of all workers once a month and monitored quality of performance.

At enrolment, information was collected on household characteristics (caste, religion, and socio-economic variables to ascertain wealth quintile), infant characteristics (birth weight and sex), birth related characteristics (place of delivery, multiple births, parity) and maternal characteristics (age, education and occupation). Infants were visited on the first and third day to document post supplementation adverse events and to obtain information on the time of breastfeeding initiation in hours after birth (if not already initiated at the enrolment visit) and colostrum intake.

Each enrolled infant was followed up till 12 months of age. Infants were contacted when aged 29 days and at 3, 6 and 12 months and at each visit, information was collected or ascertained on feeding practices, hospitalization since last visit and vital status. The study team member asked about what the infant was fed in the previous 24 hours from the time of visit, including

breast milk, plain water, animal milk, other fluids, medicines and solid food. A hospitalization was defined as either an inpatient admission (where an infant received an inpatient slip with a registration number and allotted a bed) or a stay of ≥ 6 hours duration in the hospital including the emergency services, diarrhoea management room or any paediatric wards of the institution.

Information on hospitalization was collected through hospital records and documents and in instances where a hospital record could not be found, information provided by the mother was considered. At the first follow up visit at 29 days, data on hospitalization was gathered since the infant was enrolled in the study. For subsequent follow up visits, information on hospitalization was collected since the last follow up visit.

Operational definitions used

Delayed initiation of breastfeeding - was defined as infant being initiated on breastfeeding after an hour of birth (>1 hour after birth).[15] This operational definition was same for infants born through normal vaginal and caesarean delivery. An additional outcome was also considered- "breastfeeding after 24 hours of birth", based on the findings of a recent review that indicated increased risk of mortality in infants who were initiated breastfeeding 24 hours after birth compared to those initiated ≤1 hour after birth.[16]

Exclusive breastfeeding- defined as infant being given no other food or drink, not even water, except breast milk (including milk expressed or from a wet nurse), with the exception of infant receiving oral rehydration salt (ORS), drops and syrups (vitamins, minerals and medicines) [15]

Outcomes for the secondary analysis

The primary outcome in our analysis was the association between birth weight and mortality during infancy. Secondary outcomes were association of birth weight with hospitalization and breastfeeding practices i.e. delayed initiation of breastfeeding, breastfeeding initiation after 24 hours of birth, non-exclusive breastfeeding at one and three months of age, and early termination of breastfeeding i.e. no breastfeeding at 6 and 12 months of age.

Data analysis

For the analysis, infants with information on birth weight, vital status, episodes of hospitalization, breastfeeding practices and data on covariates were included. Data analysis was performed using STATA version 11 (Stata Corporation, College Station, TX). The distribution of the data was examined. Proportions were calculated for categorical variables.

For analysis of mortality rates in the neonatal period, all babies enrolled in the trial were considered. For analysis of mortality between 29 to 90 days of age, 29 to 180 days and 29 to 365 days of age, only infants who were alive at 29 days of age were included in the analysis. Similarly, for analysis of hospitalization in the neonatal period, all infants enrolled in the trial for which data on hospitalization were available were considered. For analysis of hospitalization from 29 to 90 days of age, 29 to 180 days of age and 29 to 365 days of age, only infants who were alive at 29 days and had data on hospitalization within the specified time period were included in the analysis.

For delayed initiation of breastfeeding and breastfeeding after 24 hours of birth, infants were included in the analysis only if breastfeeding was initiated at any time after birth. For non-exclusive breastfeeding at 1 and 3 months, only infants alive at 1 month and 3 months of age, respectively, for whom breastfeeding data were available, were included in the analysis. Similarly, for no breastfeeding at 6 and 12 months of age, only infants that were alive at 6

and 12 months and information was available on their breastfeeding status were included in the analysis. Infants in whom breastfeeding was reported to be stopped at the time of visits at 6 and 12 months of age, irrespective of their prior breastfeeding status, were included under "no breastfeeding" category.

Log binomial model was used to assess the relationship between birth weight and mortality, hospitalization and breastfeeding practices. For small number of events, as it was for most of the outcomes assessed in this study, relative risk (RR) and odd ratio (OR) are usually comparable in magnitude and either of the two could be used. We used relative risk (RR) to express effect sizes as infants were prospectively followed up since enrolment into the study till 12 months of age. Birth weight was the exposure of interest and was categorized into ≥2500, 2000-2499 and <2000 grams. Birth weight category of <1500 grams was not considered because of a very small proportion of infants in this weight category (<1%). Adjustment was done for other covariates that were significant on univariate analysis at a p-value of <0.20[17,18] Covariates considered were: infant sex, multiple births, maternal age, maternal education, maternal education, parity, place of delivery, type of delivery, religion, caste , wealth quintile and administration of single dose of vitamin A (intervention in the primary trial). Reliable gestational age data based on ultrasound could not be obtained and therefore, analysis based on prematurity and intrauterine growth retardation could not be conducted. Assessment for effect modification (i.e. potential interaction) between birth weight and all covariates was done using an interaction term in the model. Likelihood ratio test was used to compare models with or without the interaction term. Post-hoc power calculation was also done for the outcomes related to mortality, hospitalization and breastfeeding practices at all the age ranges considered for the analysis. Population attributable risks were calculated against each birth weight category for each of the three outcomes i.e. mortality, hospitalization and breastfeeding practices across the different age

ranges. Population attributable risks were calculated using the following formula: P_{pop} * (RR-1)/[P_{pop} * (RR-1) + 1] ; where P_{pop}= proportion of exposed subjects in the study population and RR= risk ratio.[19,20] Kaplan-Meier survival curves for mortality were generated, by birth weight categories, for different time periods during infancy i.e. enrolment to 28 days of age, enrolment to 3 months of age, enrolment to 6 months of age and enrolment to 12 months of age.

Patient and public involvement

The current study involves secondary data analysis and therefore patients and/or public were not directly involved in the conduct of the study.

RESULTS

Characteristics of the study population

Figure 1 shows the overall flow of study participants in the primary trial. A total of 44,984 infants were recruited within 72 hours of birth, of which 65% were enrolled within 24 hours of birth. The characteristics of the population are presented in Table 1. Out of the enrolled infants, 10,658 (23.7%) weighed <2500 grams. The mean birth weight (SD) was 2732.9 (420.1) grams. Mean (SD) age of mothers was 23.9 (4.1) years. Nearly half the infants were born at home (43.3%); a third of the mothers were primiparous (32.7%) and around half of the infants were males (52.1%).

Association of birth weight with mortality during infancy

Analysis on association of birth weight with mortality outcome at all age range considered in the analysis i.e. enrolment to 28 days; 29 to 90 days; 29 to 180 days and 29 to 365 days, had a power of 100% at an alpha of 0.05. Table 2 shows the association between birth weight and mortality during the first year of life. After adjustment for covariates, being born with low birth weight, especially with a birth weight of less than 2000 gram, was associated with

higher risk of mortality compared to normal birth weight infants during the whole infancy. Supplementary table 1 shows the findings of univariate analysis of covariates with mortality outcome during the neonatal and post-neonatal period. In the neonatal period, those with birth weight between 2000-2499 grams had around 2.5 fold higher risk of death (RR 2.56; 95% CI, 2.13-3.12) while those with <2000 grams had 16 times higher risk (RR 15.64; 95% CI, 12.90-19.44). After the neonatal period, this increased risk of death in LBWs was observed between 29 to 90 days of age (RR 2.14; 95% CI, 1.74-2.58), 29 to 180 days of age (RR 2.08; 95% CI, 1.77-2.36) and 29 to 365 days of age (RR 1.92; 95% CI, 1.71-2.15). In context of mortality, the population attributable risk (PAR) for low birth weight was as high as 41% in the neonatal period and 17.6% for the post neonatal period till end of infancy. No statistically significant interaction was found between birth weight and the covariates included in the model for both neonatal and post-neonatal mortality. The interaction was specifically assessed for infant sex and was non-significant (P-value of 0.147 and 0.284 for neonatal and post-neonatal mortality respectively)**.** Figure 2 presents the Kaplan-Meier survival curves for mortality as an outcome, by birth weight categories, during different time periods of infancy. It shows that throughout the infancy, the probability of survival for those with birth weight <2000 grams was comparatively lower than those with normal birth weight i.e. ≥2500 grams.

Association of birth weight with hospitalization during infancy

For risk of hospitalization in the neonatal period (i.e. enrolment to 28 days), the comparison between normal and low birth weight infants had a power of 100%. The power was lower for analysis of risk of hospitalization between 29-90 days of age (38.8%), between 29-180 days of age (41.3%) and between 29-365 days of age (46.6%). Supplementary table 2 shows the findings of univariate analysis of covariates with hospitalization as an outcome, during the neonatal and post-neonatal period. In the neonatal period, low birth weight infants were at an increased risk for hospitalization (RR 1.86; 95% CI, 1.64-2.11) compared to normal birth

weight infants after adjustment for all potential covariates. This increased risk was observed in infants with birth weight between 2000 to 2499 grams (RR 1.73; 95% CI, 1.52-1.98) and was even higher among those <2000 grams (RR 3.13; 95% CI, 2.45-3.99) (Table 3). For the rest of infancy, although LBW infants remained at an increased risk of hospitalization, this risk was largely driven by infants <2000 grams. Overall, the relative risk of hospitalization between 29 to 365 days of age was 1.13 (95% CI, 1.05-1.21) in LBW infants and for those with birth weight <2000 grams, it was 1.74 (95% CI, 1.46-2.06). The population attributable risk for hospitalization in LBWs was around 17% in the neonatal period and reduced to only 3% in post-neonatal period till 365 days of age (Table 3). No statistically significant interaction was found between birth weight and the covariates included in the model for hospitalization. For infant sex, the interaction effect was non-significant (P-value of 0.988 and 0.621 for hospitalization in the neonatal and post-neonatal period respectively)

Association of birth weight with breastfeeding practices

Overall, close to two-thirds of LBW babies (65.9%) had delayed initiation of breastfeeding i.e. after one hour of birth. Majority of LBW babies (63.7%) were not exclusive breastfed by one and even more (78.2%) by three month of age (Table 4). At 6 and 12 months, around 8% and 18% of LBW infants were not at all breastfed, respectively. Sub-optimal breastfeeding practices were significantly associated with low birth weight, especially with a birth weight of <2000 grams, after adjustment for all possible confounding variables (Table 4). Analysis on comparison of risk for delayed initiation of breastfeeding (>1 hour after birth), breastfeeding initiation after 24 hours of birth, non-exclusive breastfeeding at 1 month of age and no breast milk feeding at 6 and 12 months of age among normal and low birth weight infants had a power of >90%; however, the power was 54.6% for risk of non-exclusive breastfeeding at 3 months of age.

Supplementary table 2 shows the findings of the univariate analysis of covariates with breastfeeding outcomes. Compared to infants with normal birth weight, those with birth weight of <2500 grams had a slightly higher risk of initiating breastfeeding after 1 hour of birth (RR 1.03; 95% CI, 1.01-1.06) and a substantially higher risk of initiating after 24 hours of birth (RR 1.64; 95% CI, 1.45-1.81).

A higher risk of non-exclusive breastfeeding at one (RR 1.07; 95% CI, 1.02-1.15) and three (RR 1.08; 95% CI, 1.03-1.14) months was observed only in infants with birth weight of <2000 grams. LBW infants were at a much higher risk of not being breastfed at all, compared to normal birth weight infants, at six months (RR 1.34; 95% CI, 1.23-1.46) and twelve months (RR 1.24; 95% CI, 1.18-1.30) of age. The risk was higher in infants with birth weight of less than 2000 grams i.e. (RR 1.49; 95% CI, 1.20-1.86) at 6 months and (RR 1.36; 95% CI, 1.18-1.56) at 12 months of age. The PAR for sub-optimal breastfeeding practices in LBW infants was around 13.3% for initiation of breastfeeding beyond 24 hours of birth; 7.2% for no breastfeeding at 6 months and 5.1% for no breastfeeding at 12 months of age. No statistically significant interaction of the covariates with birth weight was observed for any of the outcomes considered.

DISCUSSION

This secondary data analysis showed that in low birth weight infants, compared to those with normal birth weight, mortality in the neonatal as well as in the post neonatal period till 1 year of age was substantially higher. The PAR for mortality in low birth weight infants was highest in the neonatal period and declined at 12 months of age. The risk for hospitalization, reflecting severe morbidity, in both <2000 and 2000-2499 gram babies was higher compared to normal birth weight infants in the neonatal period; however, in post-neonatal period, the excess risk was seen only in <2000 gram infants. The risk of delayed initiation of breastfeeding and early termination of breastfeeding at 6 and 12 months of age was higher in

the low birth weight group and the strength of association was substantially greater for those below 2000 grams. The PAR for delayed initiation of breastfeeding beyond 24 hours of birth was around 13%. An additional 7% and 5% of "continued breastfeeding" rates at 6 and 12 months respectively could be potentially achieved by focusing on promoting breastfeeding practices in low birth weight infants, beyond the neonatal period. Achieving even this much magnitude of benefit in appropriate breastfeeding practices is crucial as early initiation of breastfeeding and continued breastfeeding during the first year of life and particularly in early infancy has been shown to be associated with improved survival and lesser morbidity.[21,22]

The findings of the study corroborate well with the previously published literature from LMICs. Katz J et al in their pooled analysis, utilising data from 20 cohorts from Asia, Africa and Latin America, documented the risk of post-neonatal mortality in preterm (RR 2.50; 95% CI, 1.48 – 4.22) and small for gestational age (RR 1.90; 95% CI, 1.32 – 2.73) infants. Their findings are similar to what we have observed in the current analysis. [7] A cohort study of LBW infants and their health outcomes in the first year of life from rural Ghana also found increased risk of mortality in LBWs in the post-neonatal period compared to normal birth weight infants. [23] Also, the risk of illness in LBW infants, compared to normal birth weight infants, declined in the post-neonatal period, similar to what the current analysis documents. [23]

In the same dataset we have also observed that LBW infants were at an increased risk of delay in receiving vaccination and being incompletely immunized by the end of infancy. Less than one-third (29.7%) of LBW infants were fully immunized by one year of age and proportion with delayed vaccination for DPT1 and DPT3 was 52% and 81% respectively. [24] In India, a little more than one-fourth of the babies are born with low birth weight.[25] The proportion of LBW varies by states and ranges from 22% to 36%.[26] Provision of quality care of small and sick babies is a priority issue in order to improve survival, growth and thrive of

this vulnerable subset of infants. Health facilities have provision for care of small and sick infants and the home visitation programme until 42 days of age aims to improve neonatal survival and reduce morbidities, although achieving adequate quality and coverage for these neonatal interventions is a persistent challenge. [11,12]

An important issue is to decide whether extended support for infants through health system is needed beyond the neonatal period. An additional question of relevance is whether post neonatal surveillance and support through continued home visitation by health care providers should be for all infants or restricted to low birth weights. Our data suggests that extended follow up and support could be for LBW infants and ideally be continued till the end of infancy owing to the high risk of mortality and sub-optimal breastfeeding practices. However in resource constrained settings, from the perspective of mortality reduction, the follow up could be at least till the first three months of life as it would provide maximum reward in terms of proportion of LBWs to be cared for (23.2%) and the corresponding reduction in mortality (PAR of 21%). The follow up for those less than 2000 grams could potentially be extended till the end of infancy as they constitute a small proportion of infants (2.5%) and corresponding reduction in mortality would be 5.6%. The extended follow up would be particularly beneficial in areas where post-neonatal mortality is high. Since wasting and stunting are also highly prevalent in India, particularly in those born with low birth weight; there is a case for extended home based surveillance and delivery of evidence based interventions to infants in most parts of the country. [27-29] The interventions could constitute monthly home visits by community health workers for growth monitoring, counselling caregivers on optimal infant care practices including recognition of illness and prompt care seeking, lactation support, promoting timely immunization, and educating caregivers on appropriate complementary feeding. Such package of interventions might be expected to improve survival, growth and development. In addition, it may lead to lower health care

costs, particularly out of pocket expenses by the family, as in many parts of India care for infant illnesses is commonly sought from private practitioners. [30,31]

The current program during the neonatal period targets all neonates which is appropriate. Our findings suggest the need for increasing the duration of contacts for the LBWs. There should be focus on improving the quality of health care provider-family interactions and follow up action when merited. The current situation where immunization is the only available contact with LBW, in the post neonatal period, leaves a large proportion of LBW infants vulnerable to premature death or poor growth and development. There is an imminent need for strengthening the existing mechanism of care and support for newborns in the first 42 days of life along with introducing additional care for LBW infants through a dedicated home based programme throughout the first year of life. Availability of Accredited Social Health Activist (ASHA) who works closer to home gives a unique opportunity to design a programme linking facility to home. [32]

An informed decision whether to focus on all infants must take into account the population attributable risk (PAR) for other adverse outcomes such as stunting. Overall, in areas of high mortality during infancy and high stunting rates, a case can be made for extended home contacts for infants beyond the neonatal period. Whether the cost-benefits may be greater and the feasibility increased by focusing such programs on LBW infants are important aspects to consider.

Strength and limitations

The findings of current analysis have adequate generalizability as the social, economic, and demographic features of the study setting are fairly representative of large parts of Southeast Asia. The strengths of the study include robust population based surveillance system, low loss to follow up and large sample size. Also, for each of the outcomes considered in the analysis, data were available for >98% of the infants, reducing the risk of selection bias. All

the infants were recruited within 72 hours of birth and their weight was measured by trained study team, thereby reducing chances of misclassification of infants by birth weight. In order to achieve adequate quality of data, the study team members were rigorously trained and underwent periodic inter and intra observer standardization exercises.

A limitation that must be considered while interpreting the findings is that the main trial did not include babies who were unable to feed in the first 72 hours of birth. This was because the trial aimed at supplementing newborns orally with vitamin A within 72 hours of birth and assess it effect on mortality within 6 months of infant age. To assess whether infants who were not enrolled in the study (i.e. those who died before contact for screening, those who could not be enrolled because of serious illness, or those who were admitted in intensive care) were of low birth weight, attempt was made to obtain birth weights for all infants who were screened but not enrolled. Weights were obtained by study workers at the visit to assess eligibility for screening. Out of the 2793 infants excluded, weights for 2087 was obtained and of these infants, 748 (36%) were low birth weight. In such babies, inadequate breastfeeding practices, morbidity and mortality would probably have been higher. Excluding them, therefore, may have made our estimates more conservative. The risk of mortality, hospitalization and sub-optimal breastfeeding practices might have been more than what we found, had such LBW babies were included in the analysis. There are some other limitations inherent to the secondary data analysis. In the primary trial, reliable data on gestational age was not obtained, making it impossible to assess, in the current analysis, how the outcomes might have been influenced by prematurity. Further, for some of the outcomes such as non-exclusive breastfeeding at 3 months of age, hospitalization between 29-90 days of age, 29-180 days of age and 29-365 days of age, the power was around 50%.

Conclusion

Low birth weight infants experience high risk of mortality, hospitalization and sub-optimal breastfeeding practices even beyond the neonatal period and therefore require continued care and support through health system in order to promote their survival. The current mechanism of home visitation program in India that focuses on the first 42 days of life may need to be extended to at least cover the first three months of infancy and if resources permit, till end of infancy.

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Table 1. Baseline characteristics of infants randomized in the primary trial (N=44,984)

Variables	n (%)
HOUSEHOLD CHARACTERISTICS	
Religion	
Hindu	34573 (76.9)
Muslim	9906 (22.0)
Others¶	505 (1.1)
Caste **	
General	12041 (26.8)
Other Backward Class (OBC)	21892 (48.7)
Scheduled Caste/Tribe (SC/ST)	11051 (24.5)
MATERNAL CHARACTERISTICS	
Mother's age (in years)	
<20	3563 (8.0)
20-30	38747 (86.1)
>30	2674 (5.9)
Mother's education (Years of schooling)	
Illiterate (0)	18814 (41.8)
1 to ≤9	16667 (37.1)
10 to <12	4383 (9.7)
≥12	5120 (11.4)
Mother's working status	
Work outside home	1142 (2.5)
Home maker	43842 (97.5)
BIRTH RELATED CHARACTERISTICS	
Place of delivery*	
Home	19478 (43.3)
Government facility	14136 (31.4)
Private facility	11326 (25.2)
Type of delivery	
Normal	42210 (93.8)
Caesarean	2592 (5.8)
Assisted	182 (0.4)
Singleton	44413 (98.7)
Multiple	571 (1.3)
Parity	
Multiparity	30257 (67.3)
Primiparity	14727 (32.7)
INFANT CHARACTERISTICS	
Sex of the baby	
Male	23418 (52.1)
Female	21566 (47.9)
Birth weight (in grams)†	
≥2500	34317 (76.3)
2000-2499	9403 (20.9)
<2000	1255 (2.8)

¶ others- Christian/Sikh/Jain/Parsi/Zoroastrian/Buddhist/neo Buddhist; **General- group that do not qualify for any of the positive discrimination schemes by Government of India (GOI), OBC- term used by the Government of India to classify castes which are socially and educationally disadvantaged, SC/ST- official designations given to groups of historically disadvantaged indigenous people in India; *remaining 44 births took place on way to health facility; † 9 infants had data missing on birth weight

Table 2. Association of mortality rates in the first year of life by birth weight in infants from rural Haryana, North India

	Number of deaths (rate per 1000 live births	Number of infants**	Univariate	Multivariate§	PAR (%)
			RR (95% CI)	RR (95% CI)	
Neonatal mortality (from enrolment to 28 days)					
Total number	---	44975			
Birth weight (grams)					
>=2500	244 (7.1)	34,317 (76.3)	Ref	Ref	-----
<2500	335 (31.4)	10658 (23.7)	4.42 (3.78-5.23)	3.92 (3.33-4.66)	41
2000-2499	181 (19.2)	9403 (20.9)	2.71 (2.27-3.31)	2.56 (2.13-3.12)*	24.6
<2000	154 (122.7)	1255 (2.8)	17.28 (14.22-20.89)	15.64 (12.90-19.44)*	29.1
Post Neonatal mortality (29-90 days)					
Total number	----	44396			
Birth weight (grams)					
>=2500	249 (7.3)	34073 (76.8)	Ref	Ref	-----
<2500	203 (19.7)	10323 (23.2)	2.69 (2.21-3.19)	2.14 (1.74-2.58)	21
2000-2499	126 (13.7)	9222 (20.7)	1.88 (1.51-2.33)	1.68 (1.36-2.08)*	12.3
<2000	77 (69.9)	1101 (2.5)	9.57 (7.32-12.07)	6.43 (4.69-8.34)*	11.9
Post Neonatal mortality (29-180 days)					
Total number	----	44396			
Birth weight (grams)					
>=2500	453 (13.3)	34073 (76.8)	Ref	Ref	-----
<2500	350 (33.9)	10323 (23.2)	2.55 (2.21-2.93)	2.08 (1.77-2.36)	20
2000-2499	249(27.0)	9222 (20.7)	2.01 (1.72-2.34)	1.78 (1.52-2.09)*	13.9
<2000	101 (91.7)	1101 (2.5)	6.89 (5.47-8.36)	4.24 (3.28-5.37)*	7.5
Post Neonatal mortality (29 to 365 days)					
Total number	---	44396			
Birth weight (grams)					
>=2500	725 (21.3)	34073 (76.8)	Ref	Ref	---
<2500	514 (49.8)	10323 (23.2)	2.33 (2.07-2.58)	1.92 (1.71-2.15)	17.6
2000-2499	392 (42.5)	9222 (20.7)	1.99 (1.76-2.24)	1.76 (1.54-1.99)	13.6
<2000	122 (110.8)	1101 (2.5)	5.20 (4.34-6.16)	3.38 (2.71-4.12)	5.6

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, caste , wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial); ** 9 infants had data missing on birth weight; *statistical significance at p-value<0.05; PAR- population attributable risk

Table 3. Association of hospitalization for severe morbidity in the first year of life, by birth weight in infants from rural Haryana, North India

	Infants with ≥1 episode (s) of hospitalization (%)	Number of infants**	Univariate	Multivariate§	PAR (%)
			Unadjusted RR (95% CI)	Adjusted RR (95% CI)	
Hospitalization from enrolment to 28 days					
Total number	---	44481			
Birth weight (grams)					
>=2500	724 (2.13)	34028 (76.5)	Ref	Ref	-----
<2500	383 (3.66)	10453 (23.5)	1.72 (1.51-1.93)	1.86 (1.64-2.11)*	16.8
2000-2499	311 (3.35)	9273 (20.8)	1.57 (1.37-1.78)	1.73 (1.52-1.98)*	13.2
<2000	72 (6.10)	1180 (2.7)	2.89 (2.27-3.63)	3.13 (2.45-3.99)*	5.4
Hospitalization in post neonatal period (29-90 days)					
Total number	---	43820			
Birth weight (grams)					
>=2500	582(1.73)	33674 (76.8)	Ref	Ref	-----
<2500	201 (1.98)	10146 (23.2)	1.15 (0.98-1.35)	1.20 (1.02-1.42)*	4.4
2000-2499	161(1.78)	9076 (20.7)	1.03 (0.87-1.22)	1.11 (0.93-1.33)	2.2
<2000	40 (3.74)	1070 (2.5)	2.17 (1.58-2.97)	2.11 (1.50-2.95)*	2.6
Hospitalization in post neonatal period (29-180 days)					
Total number	---	43056			
Birth weight (grams)					
>=2500	1444 (4.35)	33198 (77.1)	Ref	Ref	---
<2500	469 (4.76)	9860 (22.9)	1.09 (0.98-1.21)	1.15 (1.03-1.27)*	3.3
2000-2499	376 (4.24)	8863 (20.6)	0.97 (0.87-1.09)	1.05 (0.94-1.18)	1.0
<2000	93 (9.33)	997 (2.3)	2.14 (1.76-2.62)	2.08 (1.69-2.59)*	2.4
Hospitalization in post neonatal period (29 to 365 days)					
Total number	---	42708			
Birth weight (grams)					
>=2500	3046 (9.23)	32966 (77.2)	Ref	Ref	---
<2500	960 (9.86)	9742 (22.8)	1.07 (1.00-1.14)	1.13 (1.05-1.21)*	2.9
2000-2499	803 (9.17)	8761 (20.5)	0.99 (0.92-1.07)	1.07 (0.98-1.15)	1.4
<2000	157 (16.0)	981 (2.3)	1.73 (1.49-2.01)	1.74 (1.46-2.06)*	1.7

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, caste , wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial), *statistical significance at p-value<0.05; **Denotes the number of infants that were alive at the start point of analysis time frame and had data on hospitalization during the period under

consideration e.g. for analysis of hospitalization between 1 to 6 months of age, only those infants were included in analysis that were alive at 1 month of age and had data on hospitalization between 1 to 6 months of age; PAR- population attributable risk

Table 4 . Association of breastfeeding practices by birth weight in infants from rural Haryana, North India

	Number of infants with outcome of interest (%)	Total no. of infants**	Univariable	Multivariable§	PAR (%)
			RR (95% CI)	RR (95% CI)	
Delayed initiation of breastfeeding (BF initiated after 1 hour of birth)					
Total number	---	40878			
Birth weight (grams)					
>=2500	19906 (64.0)	31090 (76.1)	Ref	Ref	-----
<2500	6457 (65.9)	9788 (23.9)	1.03 (1.01-1.05)	1.03 (1.01-1.06)*	0.71
2000-2499	5685 (65.7)	8654 (21.2)	1.03 (1.01-1.05)	1.04 (1.01-1.06)*	0.84
<2000	772 (68.1)	1134 (2.7)	1.06 (1.02-1.11)	1.07 (1.03-1.15)*	0.19
Breastfeeding after 24 hours of birth					
Total number	----	40878			
Birth weight (grams)					
>=2500	1002 (3.2)	31090 (76.1)	Ref	Ref	-----
<2500	497 (5.1)	9788 (23.9)	1.59 (1.41-1.74)	1.64 (1.45-1.81)*	13.3
2000-2499	413 (4.8)	8654 (21.2)	1.49 (1.32-1.65)	1.55 (1.37-1.73)*	10.4
<2000	84 (7.4)	1134 (2.7)	2.31 (1.85-2.84)	2.43 (1.91-3.07)*	3.7
Non-exclusive breastfeeding at 1 month					
Total number	----	43656			
Birth weight (grams)					
>=2500	20491 (61.1)	33541 (76.8)	Ref	Ref	-----
<2500	6446 (63.7)	10115 (23.2)	1.04 (1.03-1.07)	1.03 (0.99-1.05)	0.69
2000-2499	5709(63.1)	9042 (20.7)	1.03 (1.02-1.05)	1.02 (0.98-1.05)	0.41
<2000	737 (68.7)	1073 (2.5)	1.12 (1.08-1.17)	1.07 (1.02-1.15)*	0.17
Non-exclusive breastfeeding at 3 month					
Total number	---	42628			
Birth weight (grams)					
>=2500	25401 (77.2)	32877 (77.1)	Ref	Ref	---
<2500	7630 (78.2)	9751 (22.9)	1.01 (1.00-1.03)	1.01 (0.98-1.03)	0.22
2000-2499	6793 (77.5)	8759 (20.6)	1.00 (0.98-1.02)	1.02 (0.97-1.06)	0.41
<2000	837 (84.4)	992 (2.3)	1.09 (1.07-1.13)	1.08 (1.03-1.14)*	0.19

No breastfeeding at 6 months					
Total number	---	42392			
Birth weight (grams)					
>=2500	1936 (5.91)	32744 (77.2)	Ref	Ref	---
<2500	778 (8.06)	9648 (22.8)	1.36 (1.26-1.49)	1.34 (1.23-1.46)*	7.2
2000-2499	682 (7.86)	8676 (20.5)	1.33 (1.22-1.45)	1.32 (1.21-1.45)*	6.1
<2000	96 (9.87)	972 (2.3)	1.67 (1.37-2.03)	1.49 (1.20-1.86)*	1.1
No breastfeeding at 12 months					
Total number	---	42492			
Birth weight (grams)					
>=2500	4776 (14.5)	32883 (77.4)	Ref	Ref	----
<2500	1791 (18.6)	9609 (22.6)	1.28 (1.22-1.35)	1.24 (1.18-1.30)*	5.1
2000-2499	1572 (18.2)	8642 (20.3)	1.26 (1.19-1.32)	1.23 (1.16-1.30)*	4.5
<2000	219 (22.7)	967 (2.3)	1.57 (1.37-1.78)	1.36 (1.18-1.56)*	0.8

§Adjusted for place of delivery, type of delivery, multiple births, mother's education, mother's age, religion, caste , wealth quintiles, parity, infant sex, administration of vitamin A (intervention in the primary trial); *statistical significance at p-value<0.05; **Denotes the total number of infants for which desired breastfeeding information was available; PAR-population attributable risk

Figure 1 . Overall flow of infants recruited in the primary trial

*LBW- Low birth Weight; NBW- Normal birth weight; 9 infants had data missing on birth weight

Figure 2 (A-D). Kaplan-Meier survival curves for mortality according to categories of birth weight for different time periods during infancy

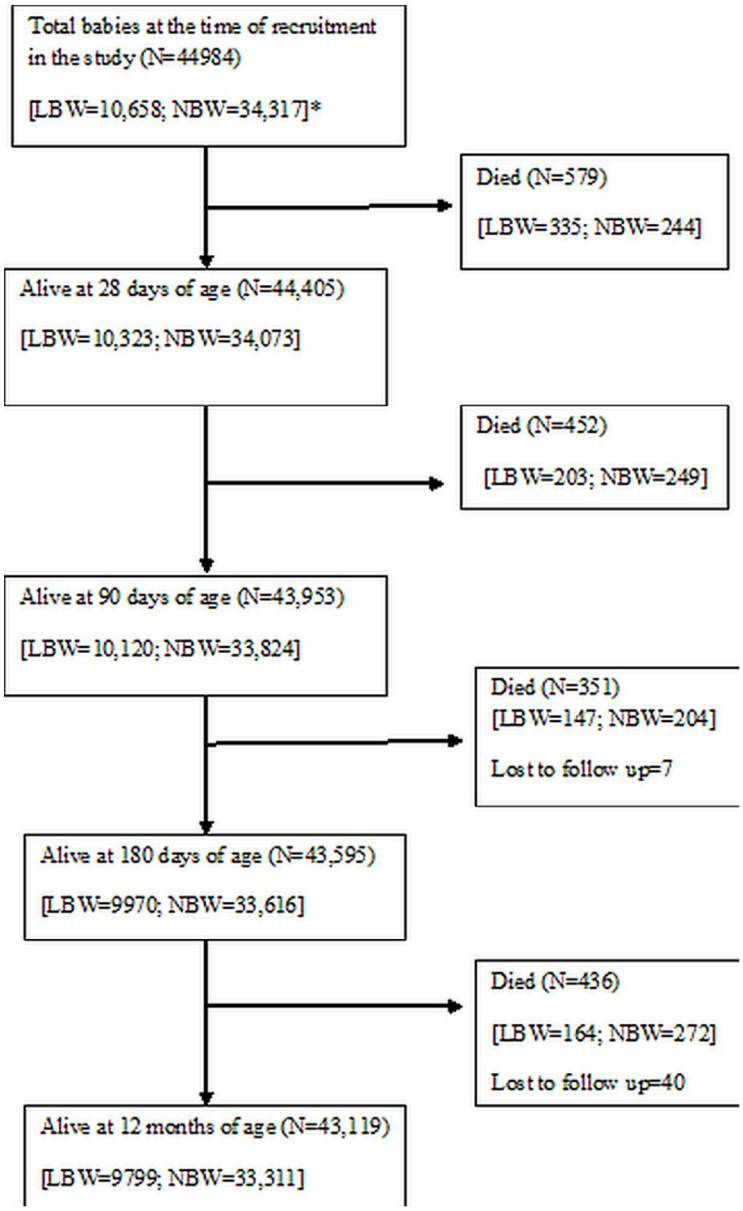

Figure 1 . Overall flow of infants recruited in the primary trial

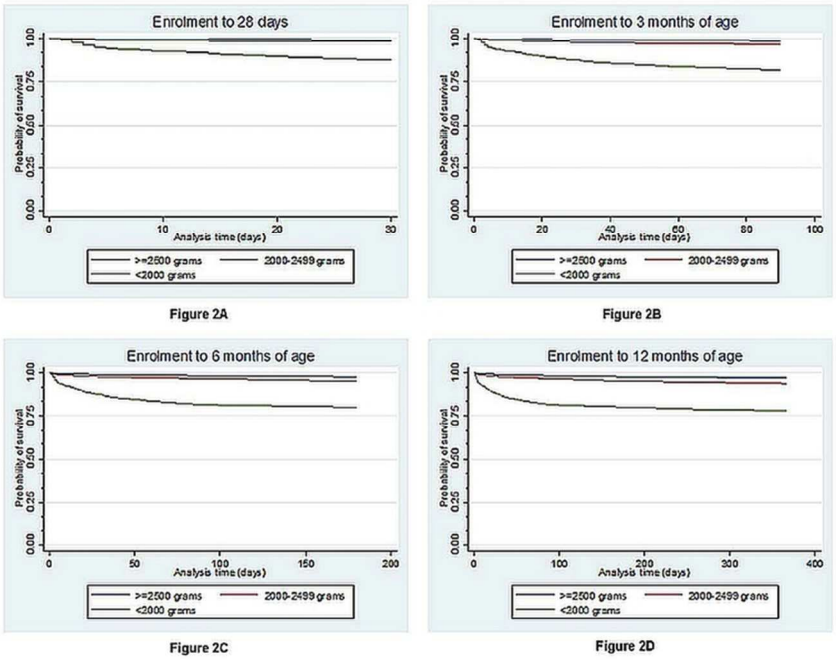

Figure 2A Figure 2B

Figure 2C Figure 2D

Kaplan-Meier survival curves for mortality according to categories of birth weight for different time periods during infancy

76x59mm (300 x 300 DPI)

Supplementary Table 1. Findings of the univariate analysis of covariates with the outcomes related to mortality and hospitalization

	Univariate analysis Crude RR (95% Confidence Intervals); P-value			
	Neonatal mortality (from enrolment to 28 days)	**Post Neonatal mortality (29-365 days)**	**Neonatal hospitalization (from enrolment to 28 days)**	**Post Neonatal hospitalization (29 to 365 days)**
Place of delivery				
Home	Ref	Ref	Ref	Ref
Government facility	0.66 (0.54, 0.80); <0.001	0.80 (0.71, 0.91); 0.001	1.17 (1.00, 1.35); 0.051	1.20 (1.12, 1.29); <0.001
Private facility	0.71 (0.58, 0.87); 0.001	0.69 (0.59, 0.79); <0.001	1.96 (1.71, 2.25); <0.001	1.61 (1.50, 1.73); <0.001
Type of delivery				
Normal	Ref	Ref	Ref	Ref
Assisted	--	0.77 (0.29, 2.05); 0.61	0.89 (0.34, 2.36); 0.82	1.00 (0.63, 1.60); 0.990
Caesarean	0.48 (0.29, 0.78); 0.003	0.63 (0.47, 0.84); 0.002	1.18 (0.94, 1.49); 0.14	1.34 (1.20, 1.49); <0.001
Multiple births				
No (singleton pregnancy)	Ref	Ref	Ref	Ref
Yes	4.31 (3.03, 6.13); <0.001	5.65 (4.58, 6.98); <0.001	2.56 (1.85, 3.56); <0.001	2.12 (1.76, 2.56); <0.001
Mother's age (yrs)				
<20	Ref	Ref	Ref	Ref
20-30	0.86 (0.65, 1.14); 0.309	0.81 (0.67, 0.97); 0.030	0.82 (0.67, 0.99); 0.041	1.13 (1.00, 1.26); 0.043
>30	1.28 (0.87, 1.78); 0.187	1.55 (1.21, 1.98); <0.001	0.52 (0.36, 0.74); <0.001	0.93 (0.78, 1.10); 0.384
Mother's education (Years of schooling)				
Illiterate (0)	Ref	Ref	Ref	Ref
1 to ≤9	0.72 (0.63, 0.89); 0.002	0.61 (0.54, 0.68); <0.001	1.57 (1.36, 1.81); <0.001	1.43 (1.33, 1.53); <0.001
10 to <12	0.47 (0.33, 0.68); <0.001	0.41 (0.32, 0.53); <0.001	2.26 (1.87, 2.73); <0.001	1.82 (1.65, 1.99); <0.001
≥12	0.43 (0.31, 0.61); <0.001	0.24 (0.18, 0.32); <0.001	2.59 (2.18, 3.08); <0.001	1.77 (1.62, 1.94); <0.001
Mother's working status				
Work outside home	Ref	Ref	Ref	Ref
Home maker	1.37 (0.76, 2.48); 0.300	0.86 (0.62, 1.19); 0.380	1.04 (0.71, 1.52); 0.831	0.98 (0.81, 1.18); 0.824
Religion				
Hindu	Ref	Ref	Ref	Ref

Muslim	1.20 (1.00, 1.45); 0.049	1.61 (1.43, 1.81); <0.001	0.38 (0.32, 0.47); <0.001	0.59 (0.54, 0.64); <0.001
Others	1.42 (0.74, 2.74); 0.287	0.99 (0.56, 1.74); 0.976	0.42 (0.19, 0.93); 0.031	0.75 (0.55, 1.03); 0.073
Caste				
General	Ref	Ref	Ref	Ref
Other Backward Class (OBC)	1.48 (1.20, 1.83); <0.001	1.66 (1.43, 1.94); <0.001	0.51 (0.44, 0.58); <0.001	0.76 (0.63, 0.72); <0.001
Scheduled Caste/Tribe (SC/ST)	1.42 (1.12, 1.80); 0.004	1.77 (1.49, 2.09); <0.001	0.60 (0.52, 0.70); <0.001	0.86 (0.80, 0.93); <0.001
Wealth quintile				
1 (Least poor)	Ref	Ref	Ref	Ref
2	1.53 (1.09, 2.13); 0.012	1.65 (1.29, 2.10); <0.001	0.84 (0.71, 0.97); 0.021	0.90 (0.83, 0.98); 0.013
3	2.39 (1.76, 3.25); <0.001	2.15 (1.70, 2.71); <0.001	0.59 (0.49, 0.70); <0.001	0.78 (0.72, 0.85); <0.001
4	2.74 (2.03, 3.70); <0.001	3.08 (2.46, 3.83); <0.001	0.54 (0.45, 0.64); <0.001	0.63 (0.58, 0.69); <0.001
5 (Poorest)	2.70 (1.99, 3.66); <0.001	4.17 (3.36, 5.16); <0.001	0.34 (0.28, 0.42); <0.001	0.49 (0.44, 0.54); <0.001
Parity				
Multiparity	Ref	Ref	Ref	Ref
Primiparity	1.14 (0.93, 1.42); 0.124	0.61 (0.53, 0.69); <0.001	1.76 (1.57, 1.98); <0.001	1.19 (1.13, 1.27); <0.001
Infant sex				
Male	Ref	Ref	Ref	Ref
Female	1.36 (1.16, 1.59); <0.001	1.56 (1.39, 1.74); <0.001	0.43 (0.37, 0.49); <0.001	0.54 (0.51, 0.58); <0.001

Supplementary Table 2. Findings of the univariate analysis of covariates with the outcomes related to breastfeeding practices

	Univariate analysis Crude RR (95% Confidence Intervals); P-value			
	Delayed initiation of breastfeeding (BF initiated after 1 hour of birth)	**BF initiated after 24 hours of birth**	**No exclusive BF at 6 months**	**No breastfeeding at 12 months**
Place of delivery				
Home	Ref	Ref	Ref	Ref
Government facility	0.88 (0.87, 0.90); <0.001	0.53 (0.46, 0.62); <0.001	0.98 (0.97, 1.00); 0.03	1.08 (1.02, 1.14); 0.005
Private facility	1.22 (1.21, 1.24); <0.001	2.17 (1.95; 2.42); <0.001	0.98 (0.97, 0.99); 0.0	1.37 (1.31, 1.45); <0.001
Type of delivery				
Normal	Ref	Ref	Ref	Ref
Assisted	1.18 (0.98, 1.40); 0.073	2.25 (1.24, 4.07); 0.008	1.05 (0.98, 1.13); 0.15	1.03 (0.73, 1.46); 0.866
Caesarean	1.40 (1.32, 1.48); <0.001	7.92 (7.01, 8.95); <0.001	1.02 (1.00, 1.05); 0.03	1.24 (1.14, 1.35); <0.001
Multiple births				
No (singleton pregnancy)	Ref	Ref	Ref	Ref
Yes	1.11 (1.05, 1.18); <0.001	2.14 (1.57, 2.93); <0.001	1.18 (1.15, 1.21); <0.001	2.39 (2.11, 2.71); <0.001
Mother's age (yrs)				
<20	Ref	Ref	Ref	Ref
20-30	0.98 (0.96, 1.01); 0.251	1.01 (0.84, 1.22); 0.882	0.95 (0.94, 0.97); <0.001	0.82 (0.76, 0.88); <0.001
>30	1.09 (1.06, 1.14); <0.001	1.51 (1.18, 1.93); 0.001	0.99 (0.96, 1.01); 0.336	0.58 (0.51, 0.68); <0.001
Mother's education (Years of schooling)				
Illiterate (0)	Ref	Ref	Ref	Ref
1 to ≤9	0.93 (0.92, 0.95); <0.001	0.72 (0.64, 0.80); <0.001	0.98 (0.96, 1.01); 0.24	1.24 (1.18, 1.32); <0.001
10 to <12	0.96 (0.93, 0.98); 0.001	0.93 (0.78, 1.10); 0.398	0.94 (0.91, 0.98); 0.003	1.46 (1.34, 1.58); <0.001
≥12	1.03 (1.00, 1.05); 0.029	1.01 (0.86, 1.18); 0.903	0.95 (0.92, 0.99); 0.01	1.50 (1.39, 1.62); <0.001
Mother's working status				
Work outside home	Ref	Ref	Ref	Ref
Home maker	0.99 (0.95, 1.05); 0.955	0.84 (0.63, 1.12); 0.239	1.03 (0.82, 1.17); 0.65	0.94 (0.82, 1.08); 0.391
Religion				
Hindu	Ref	Ref	Ref	Ref
Muslim	1.28 (1.27, 1.30); <0.001	2.08 (1.88, 2.31); <0.001	1.06 (1.05, 1.08); <0.001	0.77 (0.73, 0.82); <0.001

Others	0.92(0.84, 0.99); 0.039	0.91 (0.52, 1.59); 0.731	0.85 (0.79, 0.91); <0.001	0.98 (0.80, 1.21); 0.883
Caste				
General	Ref	Ref	Ref	Ref
Other Backward Class (OBC)	1.09 (1.08, 1.12); <0.001	1.08 (0.96, 1.20); 0.211	1.05 (1.04, 1.06); <0.001	0.77 (0.73, 0.81); <0.001
Scheduled Caste/Tribe (SC/ST)	0.93 (0.91, 0.95); <0.001	0.53 (0.45, 0.62); <0.001	1.03 (1.01, 1.05); <0.001	0.84 (0.79, 0.88); <0.001
Wealth quintile				
1 (Least poor)	Ref	Ref	Ref	Ref
2	0.93 (0.91, 0.95); <0.001	0.72 (0.62, 0.85);<0.001	1.04 (1.02, 1.06); <0.001	0.94 (0.88, 0.99); 0.034
3	0.92 (0.90, 0.95); <0.001	0.73 (0.62, 0.85); <0.001	1.02 (1.00, 1.04); 0.031	0.78 (0.73, 0.84); <0.001
4	0.93 (0.91, 0.96); <0.001	0.72 (0.61, 0.84); <0.001	1.02 (1.00, 1.03); 0.071	0.71 (0.66, 0.76); <0.001
5 (Poorest)	0.99 (0.96, 1.01); 0.188	0.95 (0.82, 1.09); 0.478	1.03 (1.01, 1.04); 0.001	0.55 (0.51, 0.58); <0.001
Parity				
Multiparity	Ref	Ref	Ref	Ref
Primiparity	1.05 (1.04, 1.07); <0.001	1.32 (1.19, 1.46); <0.001	1.05 (1.04, 1.06); <0.001	1.40 (1.34, 1.47); <0.001
Infant sex				
Male	Ref	Ref	Ref	Ref
Female	1.03 (1.01, 1.04); <0.001	0.84(0.76, 0.93); 0.001	0.99 (0.98, 1.00); 0.071	1.13 (1.08, 1.18); <0.001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page no. in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes (Page -3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes (Page -3)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes (Page 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes (Page 5)
Methods			
Study design	4	Present key elements of study design early in the paper	Yes (Page 5-9)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes (Page 5-9)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes (Page 5-9)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Yes (Page 10,21,23-26)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes (Page 5-9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes (Page 5-9)
Bias	9	Describe any efforts to address potential sources of bias	Yes (Page 5-9)
Study size	10	Explain how the study size was arrived at	Yes (Page 5-9)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes (Page 5-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes (Page 5-9)
		(*b*) Describe any methods used to examine subgroups and interactions	Yes (Page 5-9)
		(*c*) Explain how missing data were addressed	Yes (Page 5-9)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Yes (Page 5-9)
		(*e*) Describe any sensitivity analyses	We did a sub group analysis by sub-categories of low birth weight

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes (Page 20)
		(b) Give reasons for non-participation at each stage	Yes (page 10-12; page 20)
		(c) Consider use of a flow diagram	Yes (Page 20)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest	Yes (Page 23-26)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Yes (Page 23-26)
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes (Page 10-12; 23-26)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes (Page 10-12; 23-26)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes (Page 10-12; 23-26)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes (Page 10-12; 23-26)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes (Page 12-16)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes (Page 12-16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes (Page 12-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes (Page 12-16)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes (Page 1)