Soofi, S.; Ariff, S.; Sadiq, K.; Habib, A.; Bhatti, Z.; Ahmad, I.; Hussain, M.; Ali, N.; Cousens, S.; Bhutta, Z.A. (2016) [Accepted Manuscript] Evaluation of the uptake and impact of neonatal vitamin A supplementation delivered through the Lady Health Worker programme on neonatal and infant morbidity and mortality in rural Pakistan: an effectiveness trial. Archives of disease in childhood. ISSN 0003-9888 DOI: 10.1136/archdischild-2016-310542 (In Press)

Downloaded from: http://researchonline.lshtm.ac.uk/2933092/

DOI: 10.1136/archdischild-2016-310542

Usage Guidelines

Please refer to usage guidelines at http://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by-nc-nd/2.5/

Original Research

Evaluation of the uptake and impact of neonatal Vitamin A Supplementation delivered through the Lady Health Worker Program on neonatal and infant morbidity and mortality in rural Pakistan; an effectiveness trial

Sajid Soofi[1], Shabina Ariff [1], , Kamran Sadiq[1], Atif Habib [1] , Zaid Bhatti [1], Imran Ahmad [1], Masawar Hussain[1], Nabeela Ali [2], Simon Cousens [3] and Zulfiqar A. Bhutta [1,*]

[1] Women & Child Health Division, The Aga Khan University, Karachi, Pakistan

[2] John Snow International Research Institute, USA

[3] London School of Hygiene and Tropical Medicine, United Kingdom

Corresponding author*

Zulfiqar A. Bhutta

Founding Director Centre of Excellence in Women and Child Health,

Aga Khan University, Karachi, Pakistan

zulfiqar.bhutta@aku.edu

Robert Harding Chair in Global Child Health and Policy, Centre for Global Child Health, Hospital for Sick Children, Toronto, Canada

ABSTRACT

Background: Despite the evidence as to the benefits of Vitamin A supplementation (VAS) among children 6-59 months of age, the feasibility of introduction and potential benefit of vitamin A supplementation in the neonatal period in public health programs are uncertain.

Objective: The primary objective was to evalauate the feasibility and effectiveness of early neonatal Vitamin A supplementation (single dose of 50,000 international units delivered within 48-72 hours after birth) delivered through the public sector Lady Health Worker (LHW) in rural Pakistan and to document its association with reduction of mortality at 6 months of age.

Methods: A community-based, cluster randomized, placebo-controlled trial was undertaken in two districts of rural Pakistan. LHWs dispensed Vitamin A/placebo in identical capsules to newborns within 48-72 hours of birth. Follow up visits were undertaken at 1 week of age and thereafter every 4 weeks until 6 months of age**.**

Results: Of a total 15,433 consecutive pregnancies among eligible women of reproductive age, 13,225 pregnancies were registered, 12,218 live births identified and 11,028 newborns reached by LHWs. Of these 5380 (49%) received neonatal Vitamin A Supplementation and 5648 (51%) placebo. The LHWs successfully delivered the capsules to 79% of newborns within 72 hours of birth with no significant adverse effects. Although the proportion of days observed with symptoms of fever, diarrhea or rapid breathing were lower with neonatal VAS, these differences were not statistically significant. Mortality rates in the two groups were at 6 months of age .

Conclusions: While our study demonstrated that neonatal VAS was safe and could be feasibly delivered by LHWs in Pakistan as part of their early post-natal visits, the overall lack of benefit on neonatal and 6 months morbidity and mortality in our population suggests the need for further evaluation of this intervention in populations at risk.

Key Words:

Vitamin A Supplementation, Lady Health Worker, Neonatal Morbidity, Mortality

INTRODUCTION

Globally 6.3 million children die each year before reaching their fifth birthday and almost 44% of these deaths occur during the first 28 days of life (1). Annually 2.9 million neonatal deaths are reported globally that are largely preventable (2, 3). Maternal and childhood undernutrition contributes to almost 45% of child deaths and the association of vitamin A deficiency with excess risk of child morbidity and mortality after 6 months of age is well recognized. (4) Vitamin A supplementation is recommended as a key lifesaving intervention for children aged 6 to 59 months in populations at risk for vitamin A deficiency (5). Given widespread maternal vitamin A deficiency in some regions and the fact that a large proportion of child deaths occur among young infants, it is plausible that alleviation of vitamin A deficiency among young infants could be beneficial. Although some studies have reported a beneficial impact on the infant mortality in south Asia and among populations with relatively high prevalence of maternal vitamin A deficiency (6, 7) other recent studies have shown modest benefits (8).These findings cannot be generalized to the global context as other randomized controlled trials in similar settings have not shown any benefits (9-12).

Pakistan has relatively high neonatal and under-5 child mortality rates compared with other South Asian countries (13) and persistent high burden of maternal and child vitamin A deficiency at the population level (14). In 1994 the Government of Pakistan launched a national program for family planning and primary care, the so-called the Lady Health Worker (LHW) program with the objective of improving health and access to essential primary health care to rural and selected peri-urban communities. The LHWs are community-based health workers with secondary education, who are trained and employed by the Ministry of Health to deliver these services (15). Each LHW is responsible for a population of around 1000. The LHWs register all pregnant women (pregnancies) in their catchment area and as part of their assignments are supposed to undertake a postnatal visit at household level within 72 hours of birth, although the overall coverage of this intervention is very low (16). LHWs are supervised by lady health supervisors (LHS) employed at a Basic Health Unit (BHU). Each LHS is

typically responsible for 20-25 LHWs in her catchment area and supervise their overall work and monthly progress reports. The program is operational throughout the country and currently employs over 100,000 LHWs. In June 2011 as part of a constitutional amendment, the LHW program was devolved to the provinces. The national Lady Health Workers (LHW) program is the mainstay of much of primary care preventive interventions in rural settings and while a number of newborn interventions have been piloted through this program (17-19), there are none that have evaluated the feasibility and effectiveness of an early post-natal visit and provision of a vitamin A supplement.

We undertook a community-based placebo controlled cluster-randomized trial in rural Pakistan to evaluate the feasibility of delivering early neonatal vitamin A administration (single dose 50,000 international unit or placebo) through LHWs and its potential impact on health outcomes and mortality at 6 months of age. The trial is registered with Clinical Trials.gov (NCT00674089) and approved by the Ethics committees at the Aga Khan University and the National Bioethics Committee of the Government of Pakistan.

II. METHODS

CONTEXT AND POPULATION

The trial was conducted between January, 2007 and October 2010 in two rural districts, Sukkur and Jhelum, in Pakistan, representing a typical mix of periurban and rural, multiethnic populations of 1,108,000 and 1,048,000 respectively. The intervention was developed and implemented in partnership with the LHW program and the study areas selected on the basis of demographic patterns, and population mix, number of functional LHWs and approval by the LHW program for partnership and data sharing.

The LHWs and LHSs underwent three days separate training at the beginning of the project. The training focused on understanding the program objectives for commodity delivery, appropriate storage (light protection) for the capsules, transport and administration of capsules, recognition and reporting of adverse events, morbidities and hospitalizations. The LHWs were trained to record morbidities reported by mothers covering the two weeks

prior to the visit and to examine the newborn/infant for relevant morbidities using the standard WHO/IMCI algorithms for classification of respiratory tract infections, sepsis and diarrhea. Refresher trainings (1 day) were provided during the course of the study on quarterly basis.

STUDY DESIGN, CLUSTER DEFINITION, SAMPLE SIZE ESTIMATION AND ALLOCATION

A baseline census of the study areas in both districts was undertaken to enumerate households, collect socio-economic and demographic data and determine LHW density. Study clusters were defined as the catchment population of one LHW, usually an average population of 1000 covering 100 to 150 households. An external consultant generated the computerized allocation sequence of clusters to each intervention group using Epi Info 3.5.3 with restricted randomization based on population size, expected births and LHW presence.

Given the reported rural infant mortality rates from the PDHS (2006) (20), in the two districts of about 80 per thousand live births, and a projected 25% reduction in mortality at 6 months of age, we estimated that 400 clusters (200 in each group, averaging 30 births per cluster annually) would be required to demonstrate this impact with 80% power and 5% significance (21).

STUDY PROCEDURES & DATA COLLECTION

Pregnant women were registered by LHWs as part of their regular activities and standard operating procedures. Families were encouraged to report a birth as soon as it occurred and LHWs also liaised with the local traditional birth attendants to identify births. The LHWs were encouraged to visit the birth household (within 72 hours) following notification of birth to obtain written informed consent, collect information on the mother and newborn, and to administer a single dose of oral vitamin A (50,000 IU) or placebo to the baby. The LHW also counseled the mother on basic preventive measures and encouraged her to breastfeed the newborn immediately after capsule administration to ensure consumption of the entire dose. All live born infants within participating villages were potentially eligible for inclusion in the study. Infants with obvious congenital malformations and birth weight less than 1500 g, were excluded. No vitamin A doses were administered in

facilities and for facility births the LHW visited the household at least once within 72 hours of birth and if the mother and infant pair had returned from the hospital, she administered the neonatal dose.

The LHW returned empty Vitamin A capsules to the LHS who kept an inventory of the repository and provided supervision, capsule replenishment and monitored the LHWs activities as per routine. The LHW repeated the home visits on days 7 and 28 and thereafter at monthly intervals until 6 months of age. On the first follow up visit at day 7 (unless passively reported earlier by the family) the LHW collected information on any adverse events reported by the mother after vitamin A administration, and thereafter information was collected on neonatal illnesses, care seeking, hospitalizations and any deaths at the monthly visits. At each visit the infant's vital status was evaluated, signs of illness recorded, if any, and action taken as per LHW program policies.

Blood samples from a randomly selected subset of 450 infants were obtained at 6 months of age and analyzed for serum retinol concentration. The samples were collected at household level by trained phlebotomists, separated and frozen in the field and transported to the Nutrition Research lab at the Aga Khan University for analysis using standard methods (22).

MASKING, DISTRIBUTION OF CAPSULES AND QUALITY CONTROL

The vitamin A capsule contained (50,000 units) of retinol palmitate in soybean oil and the placebo contained Vitamin E (10 IU) in soybean oil. The capsules were identical in appearance (Banner Pharmacaps, Alberta, Canada) and supplied in bulk through the courtesy of the Micronutrient Initiative (Ottawa, Canada). The capsules were stored at the AKU Pharmacy with close temperature regulation and light protection, and supplied to the districts in similar containers with unique codes representing clusters and specific LHWs. The content and allocation of the capsules were masked from the investigators and field staff and the container codes were only known to the external consultant responsible for cluster randomization and the chair of the Data Safety and Monitoring Board (DSMB). The containers (Vit A and placebo) were covered with aluminum foil and transported at room temperature to the field at monthly intervals based on requirement and consumption. Research

supervisors carried out random check of Vit A stores to ensure compliance. Strict fidelity of allocation of vitamin A (or placebo) containers by LHWs was maintained by the AKU Pharmacy.

DATA CAPTURE, TRIAL SAFETY MONITORING AND ANALYSIS

Twelve independent teams of data collectors (each with six members including a supervisor) conducted a cross-sectional household survey of the entire catchment population at baseline and thereafter at three monthly intervals. The data collectors were provided with 3 days training on data collection instruments and communication skills. These teams collected information on live births, deaths, migrations and also obtained information on causes of deaths through verbal autopsies. They obtained information on receipt of Vit A by newborns from mothers/family elders. Additionally a separate data collection team visited the household at fortnightly interval to gather data on morbidity and collected details of diarrheal episodes, respiratory problems and febrile episodes that the neonate /infant encountered during the preceding 2 weeks.

The primary outcome was all-cause mortality by six months of age Secondary outcomes were common morbidities (febrile illness, diarrhea or pneumonia). Infant deaths were identified at home visits by LHWs and also verified through independent data collector team of all recruited children. In case of discrepancy between LHW record and independent study data collectors, the study supervisor verified deaths through household visits. Cause of death was determined from an independent review of verbal autopsies by two pediatricians. Disagreements were referred to a third assessor experienced in verbal autopsies.

All data files were double entered in MS Fox pro and analyzed using STATA version 12 in addition to mortality outcomes at 6 months of ageand morbidity data were analyzed . The proportion of monthly visits at which a child was reported to have had morbidity was compared between the two arms using Generalized estimating equation (GEE), account for clusters, controlling for the month of the visit (as a proxy for age).

The trial was overseen by a DSMB consisting of four members with expertise in cluster randomized trials, newborn and child health, and medical statistics, was constituted. The DSMB had access to allocation codes and

undertook blinded safety analyses to check for any excess in mortality or severe morbidity outcomes. The DSMB met thrice during the course of the study to assess progress, adverse events and key outcomes. The Chair of the DSMB gave permission to unmask the study after completion of the trial, data locking and analysis of primary outcomes. While data on primary outcomes were available by November 2011, given the LHW program devolution to the provinces in mid-2011, permission to share the results from the concerned LHW programs in Sindh and Punjab took considerably longer, and was finally received in April 2013.

RESULTS

The cross sectional surveys identified 15,433 pregnant women in the catchment area during the course of the study, of which the LHWs registered a total of 13,225 pregnant women (86%). Assessment of gestational age was based on the maternal recall of her last menstrual period. Birth outcomes were recorded for 12,218 women (92%) while 1007 (8%) were lost to follow-up and a further 374 (3.1%) pregnancies ended in stillbirths. The remaining pregnancies resulted in 11,918 live born babies. Of these, 171 live born babies (1.4%) died before the LHW conducted the first post natal visit, with the majority of the neonatal deaths (66.3% in placebo and 52.9% in neonatal Vitamin A Supplementation group) occurring within the first 24 hours of life. A further 609 (5.1 %) neonates were excluded for other reasons (Figure 1). Altogether 11,028 (92.5%) of all live born newborns were randomized to receive either placebo or neonatal Vitamin A Supplementation capsules, of which 10,286 (86.3%) infants were followed up until death or 6 months of age.

The baseline characteristics of the two study arms were comparable (Table 1). Study participants in both the groups were also comparable with respect to timing of interventions, gender and BCG vaccination status. Overall, majority of the deliveries, 55.2% occurred at home, mostly attended by TBAs. Among the newborns that had their weights assessed at birth, mean recorded birth weights were 2.82 kg in the placebo arm and 2.81 kg in neonatal Vitamin A Supplementation arm. Overall 8.3% of infants were low birth weight (< 2.5 kg) in placebo arm compared with and 9.3% in neonatal Vitamin A Supplementation. (Table 2). Newborn in the community

receive first dose of polio and BCG at the BHUs by government employed vaccinators and the BCG vaccination status for the two groups was comparable.

The LHWs successfully delivered the capsules to the majority (80%) of newborns (neonatal Vitamin A Supplementation /placebo) within 72 hours of birth, of them 60% received these within 24 hours. A total of 26 adverse events were documented in the both the groups, neonatal Vitamin A Supplementation 10, placebo 16 (p=0.19). Of the ten adverse events in the neonatal Vitamin A Supplementation group, seven were diarrheal episodes. Only one case of bulging fontanel was reported in each group (Table 3).

We did not measure maternal or neonatal serum retinol concentrations at birth or recruitment. However, among the subset of 449 infants sampled at 6 months of age, there was no evidence of a difference in mean serum retinol concentrations between the two groups (Table 4). However, the proportion of severe retinol deficiency was significantly lower among supplemented infants.

There were no differences in reported morbidities between the two arms of the study. The morbidity rates of diarrheal episodes, fever and rapid breathing and severe pneumonia were similar in both groups (Table 5). Neonatal deaths (0-28days) per protocol were comparable in both the placebo and intervention arms (48 vs 57 p value 0.59). Similarly no difference was documented in (0-6 months) mortality also (115 vs 128 p value 0.64).The Intention to treat analysis (ITT)) also revealed similar results (Table 6).

DISCUSSION

Our findings show that it was feasible for LHWs in Pakistan to deliver vitamin A supplements to newborn infants within 72 hours of birth. Given the importance attached to postnatal visits (23) in terms of impact on newborn survival, this is an important step in developing integrated packages for preventive care after birth. The repertoire of interventions that can be implemented in the immediate postnatal period and the first few days of life e.g. cord chlorhexidine application (19), breastfeeding promotion and oral polio, BCG and hepatitis B vaccines, the addition of neonatal vitamin A dosing to these interventions is both feasible and potentially cost-

effective. The LHWs and families did not report any significant adverse effects with the 50,000 unit dosing. Only one case was reported to have bulging fontanel, which self-resolved within 72 hours, while another case of vomiting and suspected seizures was found to be well at examination and resolved within 24 hours. These data suggest that overall neonatal Vitamin A Supplementation is a safe intervention that can be administered by CHWs in community settings.

The key question is if the intervention is effective with health and survival benefits. We did not find any impact on mortality at 6 months of age and the observed effects on morbidity were also marginal and non-significant. Several limitations must be recognized in our study. Our trial was designed to assess the feasibility and effectiveness in a large rural district but had a smaller sample size than other similar studies (7). We did not measure vitamin A status in mothers or newborns at baseline and hence it is difficult to ascertain the extent to which biochemical vitamin A deficiency was widespread in the target population .. However, a recent national nutrition survey including these very districts has highlighted vitamin A deficiency on serum retinol estimation at 42.5% and 54% among women of reproductive age and children under 5 from this district respectively (14).

Similar burden has been documented in Africa with Vitamn A deficiency as high as 43% with higher prevalence in the rural population,Others have demonstrated somewhat lower levels . (24, 25)

Our findings of the lack of significant benefit of neonatal vitamin A supplementation on survival at 6 months of age is at variance with other studies in South Asia (6, 7, 8). However, other studies in Africa have failed to show any benefits of neonatal vitamin A supplementation on survival (10, 26). Although some reviews have failed to show any mortality benefit of neonatal vitamin A dosing (27), our previous assessment of the evidence suggested geographic variation in response to neonatal vitamin A supplementation which could relate to prevalent maternal vitamin A or multiple micronutrient deficiencies (28, 29). Although some gender related differences in outcomes and survival have been reported (30), we did not find any differences in outcomes among female infants. Previous studies of neonatal vitamin A supplementation have also reported mixed results

on morbidity patterns. In Indonesia, neonatal vitamin A supplementation was associated with reduced number of clinic visits (29). Our data on morbidity patterns also did not show any reduction in morbidity rates or hospitalizations with neonatal vitamin A supplementation.

Breast-feeding provides protection against vitamin A deficiency even in populations where deficiency may be endemic. Our study population had almost universal breast feeding (98%) in both the placebo and supplemented arms. The lack of apparent benefit on mortality may also be because of protection from vitamin A deficiency conferred by exclusive breast-feeding early in life. The blood samples at 6 month of age did show an impact on the proportion with severe vitamin A deficiency among the supplemented infants.

Conclusion:

We conclude that the delivery and distribution of Vit A was feasible through the public sector LHWs. However recommendations as to its inclusion in the repertoire of interventions must await further evidence of benefits and risks. Our study did not show any benefit on infant survival Two of three large trials evaluating impact of vitamin A on infant mortality have been published recently, demonstrating no benefits (10, 26), although the study in India was associated with a 10% reduction in mortality at six months of age (8), once again lending support to the contention that the intervention may be relevant in populations with varying rates of maternal nutritional risks and vitamin A deficiency. Further recommendations on neonatal vitamin A supplementation must therefore await additional contextual analysis and targeting to populations at greatest risk, as well as comparison with alternative strategies (29, 32).

Role of the funding source:

This study was funded by PAIMAN (Pakistan Initiative for Mothers and Newborns) /John Snow Inc via grant funded by USAID, Award Number: Sub-agreement #: 36098-01 (USAID cooperative agreement # 391-A-00-05-

01037-00). The funding body provided clearance for the project design but apart from field visits to review progress did not influence the field trial or the data analysis procedures.

Registration ID:

The trial is registered as NCT00674089.

Conflicts of interest:

All other authors declare that they have no conflict of interest.

Contribution statements:

ZAB conceptualized the study and as principal investigator involved in all aspects of this study. SS was study coordinator and oversaw study implementation. SA and SS wrote the first draft and were responsible for subsequent and final versions of the manuscript. ZAB reviewed & finalized the final version. KS, AH & NA were involved in study design, analysis plan and interpretation of data. MH & SH implemented the study at field site. IA & ZB oversaw the data management, coordination and data cleaning. SC was involved in data analysis and interpretation of data. All authors reviewed and approved the final manuscript.

Ethical approval:

This study was approved by the Ethical Review Committee (ERC) of Aga Khan University, Karachi, Pakistan. All the respondents gave informed consent prior to completing the interviews.

Acknowledgement:

We thank Lady Health Workers of National Program for Family Planning and Primary Care for their exceptional support and all the staff of the study for their hard work. We would also like to thank Mr Asghar Ali Khan, Senior Manager Grants and Dr Farhana Shahid, Dr Sunil Hotwani, study supervisors, Mr Didar Alam, Coordinator, Research Labs at Aga Khan University for facilitation they provided for the study. We also acknowledge Prof Qamaruddin Nizami contribution in masking and randomization process.

References

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, Cousens S, Mathers C, Black RE. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385:430-40
2. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P, Mathers C, Cousens SN; Lancet Every Newborn Study Group. Every Newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384:189-205.
3. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, Sankar MJ, Blencowe H, Rizvi A, Chou VB, Walker N; Lancet Newborn Interventions Review Group; Lancet Every Newborn Study Group. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? Lancet. 2014;384:347-70.
4. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013 Aug 3; 382:427-51.
5. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE; Lancet Nutrition Interventions Review Group; Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013;382:452-77.
6. Rahmathullah L, Tielsch JM, Thulasiraj RD, Katz J, Coles C, Devi S, John R, Prakash K, Sadanand AV, Edwin N, Kamaraj C. Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomized trial in southern India. BMJ. 2003;327:254.
7. Klemm RD, Labrique AB, Christian P, Rashid M, Shamim AA, Katz J, Sommer A, West KP Jr. Newborn vitamin A supplementation reduced infant mortality in rural Bangladesh. Pediatrics. 2008;122(1):e242-50
8. Mazumder S, Taneja S, Bhatia K, Yoshida S, Kaur J, Dube B, Toteja GS, Bahl R, Fontaine O, Martines J, Bhandari N; Neovita India Study Group. Efficacy of early neonatal supplementation with vitamin A to reduce mortality in infancy in Haryana, India (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:1333-42

9. Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D, the DEVTA (Deworming and Enhanced Vitamin A) team .Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. Lancet. 2013;381:1469-77.
10. Edmond KM, Newton S, Shannon C, O'Leary M, Hurt L, Thomas G, Amenga-Etego S, Tawiah-Agyemang C, Gram L, Hurt CN, Bahl R, Owusu-Agyei S, Kirkwood BR. Effect of early neonatal vitamin A supplementation on mortality during infancy in Ghana (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:1315-23.
11. West KP Jr., Christian P, Labrique AB, Rashid M, Shamim AA, Klemm RD, et al. Effects of vitamin A or beta carotene supplementation on pregnancy-related mortality and infant mortality in rural Bangladesh: a cluster randomized trial. JAMA. 2011 May 18;305(19):1986-95.
12. Benn CS, Fisker AB, Jorgensen MJ, Aaby P. Conflicting evidence for neonatal vitamin A supplementation. Vaccine. 2008;26:4111-12.
13. National Institute of Population Studies (NIPS) [Pakistan] and ICF International. 2013. Pakistan Demographic and Health Survey 2012-13. Islamabad, Pakistan, and Calverton, Maryland, USA: NIPS and ICF International. [http://www.nips.org.pk/abstract_files/PDHS%20Final%20Report%20as%20of%20Jan%2022-2014.pdf]
14. Pakistan National Nutrition survey 2011: Nutrition Wing, Ministry of Health. Pakistan. Hafeez A, Mohamud BK, Shiekh MR, Shah SA, Jooma R. Lady health workers programme in Pakistan: challenges, achievements and the way forward. JPMA The Journal of the Pakistan Medical Association. 2011;61:210-5.
15. Bhutta ZA, Hafeez A, Rizvi A, Ali N, Khan A, Ahmad F, Bhutta S, Hazir T, Zaidi A, Jafarey SN. Reproductive, maternal, newborn, and child health in Pakistan: challenges and opportunities. Lancet. 2013;381:2207-18
16. Bhutta ZA, Soofi S, Cousens S, Mohammad S, Memon ZA, Ali I, et al. Improvement of perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. Lancet. 2011;377:403-12.

17. Turab A, Ariff S, Habib MA, Ahmed I, Hussain M, Rashid A, et al. Improved accessibility of emergency obstetrics and newborn care (EmONC) services for maternal and newborn health: a community based project. BMC pregnancy and childbirth. 2013;13:136.
18. Soofi S, Cousens S, Imdad A, Bhutto N, Ali N, Bhutta ZA. Topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, cluster-randomised trial. Lancet. 2012; 379:1029-36.
19. National Institute of Population Studies (NIPS) [Pakistan], and Macro International Inc. 2008. Pakistan Demographic and Health Survey 2006-07. Islamabad, Pakistan: National Institute of Population Studies and Macro International Inc. [http://dhsprogram.com/pubs/pdf/FR200/FR200.pdf]
20. Hayes RJ, Moulton LH. Cluster randomised trials. London, UK: Chapman and Hall/CRC Interdisciplinary Statistics, 2008.
21. Teglia CM, Gil García MD, Galera MM, Goicoechea HC. Enhanced high-performance liquid chromatography method for the determination of retinoic acid in plasma. Development, optimization and validation. J Chromatogr A. 2014;1353:40-8
22. Lassi ZS, Middleton PF, Crowther C, Bhutta ZA. Interventions to Improve Neonatal Health and Later Survival: An Overview of Systematic Reviews. EBioMedicine. 2015;2:983-98
23. Benn CS, Fisker AB, Napirna BM, Roth A, Diness BR, Lausch KR, Ravn H, Yazdanbakhsh M, Rodrigues A, Whittle H, Aaby P. Vitamin A supplementation and BCG vaccination at birth in low birthweight neonates: two by two factorial randomized controlled trial. BMJ. 2010 Mar 9;340:c1101. doi: 10.1136/bmj.c1101
24. Christine Hofz; Justine Chileshe et al ,Vitamin A intake and infection are associated with plasma retinol among preschool children in rural Zambia, Public health NUTRITION 15(9),1688-1696
25. Busie B.Maziya-Dixon, Issac O.Akineyele et al .Vitamin A Deficiency Is Prevalent in Children Less than 5 years of age in Nigeria .The Journal of Nutrition Community and International Nutrition. AMERICAN Society of Nutrition

26. Masanja H, Smith ER, Muhihi A, Briegleb C, Mshamu S, Ruben J, Noor RA, Khudyakov P, Yoshida S, Martines J, Bahl R, Fawzi WW; Neovita Tanzania Study Group. Effect of neonatal vitamin A supplementation on mortality in infants in Tanzania (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:1324-32
27. Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. BMJ (Clinical research ed). 2009;338:b919
28. Haider BA, Bhutta ZA. Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD006980. doi: 10.1002/14651858
29. Haider BA, Bhutta ZA. Neonatal vitamin A supplementation: time to move on. Lancet. 2015;385:1268-71.
30. Benn CS, Aaby P, Arts RJ, Jensen KJ, Netea MG, Fisker AB. An enigma: why vitamin A supplementation does not always reduce mortality even though vitamin A deficiency is associated with increased mortality. Int J Epidemiol. 2015;44:906-18
31. Humphrey JH, Agoestina T, Wu L, Usman A, Nurachim M, Subardja D, Hidayat S, Tielsch J, West KP Jr, Sommer A. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. J Pediatr. 1996;128:489-96
32. S Basu, B Sengupta, P K Roy Paladhi. Single megadose vitamin A supplementation of Indian mothers and morbidity in breastfed young infants. Postgrad Med J 2003;79:397–402.

Table 1: Socio-demographic of the infant's families pre-randomization (Baseline survey), n (%)

Characteristic	Placebo (n=25474)	VAS (n=28431)
Married women aged 15–49 years	23877	26076
Median age (IQR) in years	30 (25 - 40)	31 (26 - 40)
Maternal literacy	6623 (28%)	7544 (29%)
Household density	6.2	6.1
Monthly household income		
≤ 6000 PKR	16437/25033 (67%)	18814/28260 (68%)
> 6000 PKR	8227/25033 (33%)	9028/28260 (32%)
Median (IQR)	5000 (3000 - 8000)	5000 (3000 - 7000)
Nature of construction of household		
Pucca (concrete)	14289/25431 (56%)	12015/28390 (42%)
Semi-pucca	5063/25431 (20%)	11251/28390 (40%)
Katcha	5623/25431 (22%)	4774/28390 (17%)
Others	456/25431 (2%)	350/28390 (1%)
Living rooms in the house		
One	8800/25191 (35%)	8699/28272 (31%)
Two or more	16365/25191 (65%)	19561/28272 (69%)
Main cooking fuel		
Electricity	3279/25474 (13%)	3742/28431 (13%)
Natural Gas	4829/25474 (19%)	3590/28431 (13%)
Firewood	17094/25474 (67%)	20764/28431 (73%)
Others	216/25474 (1%)	289/28431 (1%)
Household with electricity	24470/25425(96%)	27816/28399(98%)
Main drinking water source		
Well/ Hand pump	4552/25429 (18%)	4826/28387 (17%)
Communal tap/Motor pump	14978/25429 (59%)	17032/28387 (60%)
Others	5900/25429 (23%)	6529/28387 (23%)
Type of latrine		
Open fields	9133/25427 (36%)	9918/28385 (35%)
Pit latrine	3983/25427 (16%)	4449/28385 (16%)

WC connected to public sewerage / open drains	12253/25427 (48%)	13970/28385 (49%)

Data are n, n (%) or median (IQR)

N.B. Denominator can be varied due to not reported responses

Table 2: Baseline characteristics of mothers and Delivery and Newborn Care Practices (post randomization)

Characteristic	Placebo	VAS
Baseline characteristics of mothers	**(n=5962)**	**(n=6256)**
ANC visits during current pregnancy		
Never	474/5693 (8%)	551/5947 (9%)
1-3	2658/5693 (47%)	2608/5947 (44%)
> 3	2561/5693 (45%)	2788/5947 (47%)
Iron or multivitamin supplementation during current pregnancy		
Yes	4342/5962 (73%)	4579/6256 (73%)
Addiction during the pregnancy period		
Tobacco	64(1%)	52(1%)
Non-smoking tobacco‡	182(3%)	143(2%)
Reproductive history		
Gravida Mean (SD)	2.51 (2.57)	2.49 (2.78)
Delivery and Newborn Care Practices	**(n=5380)**	**(n=5648)**
Place of delivery		
At home	2892/5341 (54%)	3169/5632 (56%)
Govt. Health facility	715/5341 (13%)	838/5632 (15%)
Private Hospital	930/5341 (17%)	908/5632 (16%)
Private clinic	804/5341 (15%)	717/5632 (13%)
Delivery attended		
Skilled provider*	2779/5346 (52%)	2800/5628 (50%)
Unskilled	339/5346 (48%)	2828/5628 (50%)
Use of Clean Delivery Kits	3508/5291(66%)	3604/5420 (67%)
Gender of the child		
Male	2772/5378 (52%)	2965/5645 (53%)
Female	2606/5378 (49%)	2680/5645 (48%)
Birth weight (kg)		
< 2.5	306/3693(8.%)	331/3549(9%)
≥2.5	3387/3693 (92%)	3218/3549 (91%)
Birth weight Mean (SD) kg	2.82 (0.72)	2.81 (0.74)
BCG given to newborn after birth		
Yes	1614/5370 (30%)	1629/5630 (29%)

Data are n, n (%), or mean (SD), ǂpan, niswar & gutka, * Doctor , Nurse & LHV

N.B. Denominator can be varied due to not reported responses

Table 3: Adverse events following Vitamin A supplementation, n (%)

	Placebo	VAS	p-value
Adverse event reported within one week of supplementation	16/5380 (0.3%) (95%CI 0.2-0.5)	10/5648 (0.2%) (95%CI 0.1-0.3)	0.2
Distribution of Adverse Event			
Loose Motion	8/16(50%) (95%CI 23-77)	7/10 (75%) (95%CI 39-100)	
Vomiting	2/16 (12.5%) (95%CI 0-30)	1/10 (10.0%) (95%CI 0-31)	
Bulging fontanel	1/16 (6%) (95%CI 0-19)	1/10 (10%) (95%CI 0-31)	
Unconsciousness	1/16 (6%) (95%CI 0-19)	0/10 (0%) (95%CI - -)	
Seizures	1/16 (6%) (95%CI 0-19)	1/10 (10%) (95%CI 0-31)	
Fever	3/16 (19%) (95%CI 0-40)	0/10 (0%) (95%CI - -)	
Hospitalization during first 6 months of life	185/5380 (3.4%) (95%CI 2.9-3.9)	185/5648 (3.3%) (95%CI 2.8-3.7)	0.6

Data are n, n (%)

Table 4: Serum Retinol level at 6 months of age

	Placebo (n=219)	VAS (n=230)	p-value
Retinol (µg/dl)			
Severe deficiency (<10 µg/dL)	19/219 (9%) (95%CI 5-12)	79/230 (4%) (95%CI 1-6)	0.04
Deficiency (<20 µg/dL)	82/219 (37%) (95%CI 31-44)	79/230 (34%) (95%CI 28-41)	0.5
Mean (SE)	25.7 (0.87) (95%CI 24-28)	26.9 (0.99) (95%CI 25-29)	0.4
Median (QR)	23.7 (16.4, 33.3)	23.7 (16.8, 32.8)	
Data are n, n (%), or mean (SE) or median (IQR)			

Table 5: Reported morbidities by treatment arm

	Placebo	VAS	Odds ratio[1] (VAS versus Placebo) (95% CI)
Proportion of monthly visits at which child was reported to have been ill in preceding 30 days			
Number of monthly visits completed	26571	27465	
Fever	8130/26571 (31%)	7928/27465 (29%)	0.94 (0.76, 1.16)) P=0.5
Diarrhoea	2,609/26571 (10%)	2,272/27465 (8%)	0.78 (0.57, 1.08) P=0.1
Rapid breathing	740/26571 (2.8%)	617 /27465 (2.3%)	0.92 (0.55, 1.53) P=0.7
Severe Pneumonia2	245/26571 (0.9%)	121/27465 (0.4%)	0.42 (0.16, 1.11) P=0.1

1: Odds ratio estimated using Generalized estimating equation (GEE) to account for the cluster randomisation and adjusted for month of visit

Data are n, n (%), or mean proportion of days with illness

Table 6: Effect of vitamin A post supplementation on primary outcome: overall and stratified by sex

Mortality (post supplementation)	Number of newborns supplemented				Risk per 1,000 live births		Odds Ratio	p-value	Effect size (95% CI)
	Placebo		VAS		Placebo	VAS	(95% CI)		
	Events	No. of newborns	Events	No. of newborns					
a. Neonatal Mortality (0-28 days)									
Overall	**48**	**5380**	**57**	**5648**	**9 (95%CI 7-12)**	**10 (95%CI 8-13)**	**1.13 (0.76, 1.66)**	**0.6**	**0.06 (-0.14, 0.28)**
Male	21	2774	26	2966	7.6 (95%CI 5-12)	8.8 (95%CI 6-13)	1.15 (0.65, 2.06)	0.6	0.08 (-0.23, 0.39)
Female	27	2606	31	2682	10.4 (95%CI 7-15)	11.6 (95%CI 8-16)	1.11 (0.66, 1.87)	0.7	0.06 (-0.22, 0.34)
b. Mortality (0 - 6 months)									
Overall	**115**	**5380**	**128**	**5648**	**21 (95%CI 18-26)**	**23 (95%CI 19-27)**	**1.06 (0.82, 1.37)**	**0.6**	**0.03 (-0.10, 0.17)**
Male	49	2774	58	2966	17.7 (95%CI 13-23)	19.6 (95%CI 15-25)	1.10 (0.75, 1.62)	0.6	0.05 (-0.15, 0.26)
Female	66	2606	70	2682	25.3 (95%CI 20-32)	26.1 (95%CI 21-33)	1.03 (0.73, 1.44)	0.9	0.01 (-0.17, 0.20)
Mortality (pre and post supplementation)									
c. Neonatal Mortality (0-28 days)									
Overall	**134**	**5706**	**142**	**5970**	**23 (95%CI 20-28)**	**24 (95%CI 20-28)**	**1.01 (0.80, 1.27)**	**0.9**	**0.007 (-0.12. 0.13)**
Male	73	2959	75	3145	25 (95%CI 20-31)	24 (95%CI 19-30)	0.96 (0.69, 1.33)	0.8	-0.01 (-0.19, 0.16)
Female	61	2747	67	2825	22.2 (95%CI 17-28)	23.7 (95%CI 19-30)	1.06 (0.75, 1.52)	0.7	0.03 (-0.15, 0.23)
d. Mortality (0 - 6 months)									
Overall	**201**	**5706**	**213**	**5970**	**35 (95%CI 31-40)**	**36 (95%CI 31-41)**	**1.03 (0.83, 1.23)**	**0.9**	**0.007 (-0.10, 0.11)**

Male	101	2959	107	3145	34 (95%CI 28-41)	34 (95%CI 28-41)	0.99 (0.75, 1.31)	1.0	-0.002 (-0.15, 0.15)
Female	100	2747	106	2825	36 (95%CI 30-44)	38 (95%CI 31-45)	1.03 (0.78, 1.36)	0.8	0.01 (-0.13,0.17)