Incidence, Severity and Epidemiology of Vitamin K Deficiency Bleeding among Infants Born in Rural Bangladesh

By

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Reg. No. 05/2004-05

Academic Year: 2004-05

A dissertation submitted to the Dhaka University, Faculty of Postgraduate Medical Science and Research in conformity with the requirements for the degree of Doctor of Philosophy

Dhaka, Bangladesh

June, 2008

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To Whom It May Concern

Subject: Certification of the Research Work (Reg. No. 05/2004-05, Academic Yr 2004-05) of Md Mahbubur Rashid for the PhD Dissertation

This is to certify that the research work titled "Incidence, Severity and Epidemiology of Vitamin K Deficiency Bleeding among Infants Born in Rural Bangladesh" was conducted by Md. Mahbubur Rashid, PhD candidate, Faculty of Post Graduate Medical Science and Research and Reg. No. 05/2004-05, Academic Year 2004-05, under my close supervision. Prof. Keith P. West Jr., George G. Graham Professor of Infant and Child Nutrition, Center for Human Nutrition, Department of International Health, Johns Hopkins University, USA was his another supervisor. He satisfactorily completed all the required revisions and modifications suggested by the examiners in this resubmission. This is an original research work and no part of this research was used for award of any degree anywhere.

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Declaration of the Candidate

The work presented in this thesis is an original and has not been submitted by me to any university or institute for the award of any degree or diploma. The title "Incidence, Severity and Epidemiology of Vitamin K Deficiency Bleeding among Infants Born in Rural Bangladesh" is submitted by me for the award of degree on Doctor of Philosophy at the University of Dhaka, Bangladesh is based upon on my own work. The work was carried out under the supervision of Prof. Mamunar Rashid, Professor of Community Medicine, Ibrahim Medical College and Prof. Keith P. West Jr. George G. Graham Professor of Infant and Child Nutrition, Center for Human Nutrition, Department of International Health, Johns Hopkins University Bloomberg School of Public Health. That neither of this thesis nor any part of it has been submitted for the award of any degree or diploma anywhere.

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GLOSSARY

AI	Adequate Intake
BAEC	Bangladesh Atomic Energy Commission
BMRC	Bangladesh Medical Research Council
CFR	Case Fatality Rates
CI	Confidence Interval
DGLV	Dark Green Leafy Vegetables
DIC	Disseminated Intravascular Coagulation
EBF	Exclusive Breastfeeding
ELISA	Enzyme Linked Immunoassay
FWC	Family Welfare Center
GIS	Geographic Information System
HDN	Hemorrhagic Disease of Newborn
I6MOP	Infant 6 Month Post Partum Form
IAEA	International Atomic Energy Commission
IQR	Inter Quartile Range
ISTH	International Society of Thrombosis and Hemostasis
IVBA	Infant Verbal Autopsies
JHU	Johns Hopkins University
LBW	Low Birth Weight
MA	Medical Assistant
MCWC	Maternal and Child Welfare Center

MUAC	Mid Upper Arm Circumference
NEC	Necrotizing Enterocolities
OR	Odds Ratio
PIVKA-II	Protein Induced in Vitamin K Absence
RR	Relative Risk
SACMO	Sub Assistant Community Medical Officer
SD	Standard Deviation
TBA	Traditional Birth Attendants
THC	Thana Health Complex
UBHPP	USAID and Bangladesh Health and Population
Program	
USA	United States of America
USAID	United States Agency for International Development
VKDB	Vitamin K Deficiency Bleeding
vWD	von Willebrand Disease

ACKNOWLEDGEMENT

First and foremost, I would like to express my deepest appreciation to my supervisors Prof. Mamunar Rashid and Prof. Keith P. West Jr. for their visionary mentorship, excellent suggestions, constructive criticisms, and particularly for making time for reviewing the thesis despite their very tight schedules. Without their active guidance and encouragement, it would not have been possible for me to complete this dissertation.

I acknowledge the encouragement and insightful suggestions that I received from Prof. Parul Christian and Dr. Rolf Klemm, Johns Hopkins University. I appreciate the active support and inspiration that I received from Dr. Alain B. Labrique to complete my doctoral study. I would like to thank Dr. Kerry Schulze for analyzing the PIVKA-II samples. I particularly acknowledge Snaebjorn Gunnsteinsson's assistance in my multivariate analyses. I thank Sucheta Mehra for helping me in collecting references from overseas libraries.

I would also like to express my indebtedness to my colleagues Abu Ahmed Shamim, Akteruzzaman and Abdul Jabbar for their support and taking some of my responsibilities during the writing phase of the dissertation. I would wish to thank Drs. Barkat and Hasmot, who offered their comments on my initial drafts. I thank Kajol Kumar for his excellent desktop help. My profound appreciation goes to all of my JiVitA field colleagues who maintained the highest quality in data collection throughout the study period.

I also acknowledge the cooperation that I received from the Dean's office of the Postgraduate Medical Science Faculty and from the Dhaka University at different time periods.

Most importantly, I wish to express my gratefulness to Shammi (wife), Sunny (son), Samin and Shee (daughters), and to my parents for their love, patience, kind understanding and constant encouragements during the entire period of this doctoral study.

I dedicate this dissertation to the infants who died needlessly from a preventable cause, and thankfully acknowledge the debt to the mothers who provided the data allowing me to pursue my doctoral degree in public health.

Md. Mahbubur Rashid

ABSTRACT

Background: Newborn infants encounter a well-established risk of vitamin K deficiency bleeding (VKDB) due to poor placental transfer of vitamin K, low concentration of plasma clotting factors and low vitamin K content of breast milk. VKDB is a public health concern in the developed world and reported to be at a public health significance level in neighboring India, Thailand, Vietnam, Malaysia and China. Based on the literature, the prevalence of VKDB appears to be 4.9 - 14.3 per 1000 infants, while the case fatality rate for VKDB is high and many infants are left with long term sequels due to bleeding into the central nervous system. Considering its importance, the possible negative role of exclusive breastfeeding (EBF), existing gaps in knowledge, and prevailing conditions that may increase the risk for vitamin K deficiency bleeding in the developing world, it was strongly felt that a study be carried out on an urgent basis on the magnitude of this preventable problem in rural Bangladesh.

Objectives: To assess the incidence, fatality, risk factors and extent of maternal vitamin K deficiency associated with infantile bleeding disorders.

Methods: A non-concurrent prospective design to collect data related to bleeding symptoms, morbidity and survival of infants who were participating in the JiVitA-1 trial, was carried out in Gaibandha and Rangpur Districts. Data for two cohorts, of 26,705 surviving and 3,139 deceased infants, were analyzed for estimating incidence rates, case fatality rates and odds ratios for infant bleeding, adjusted for potential confounders. Laboratory analyses of 3rd trimester and 3-month postpartum PIVKA-II levels (protein inducted in vitamin K absence) were conducted in a sub-sample of 295 mothers.

Results: The over all incidence rate of any bleeding symptoms (combined) was 102.0 per 1000 infants and the rate was comparatively higher among deceased infants (207 vs. 89.7 per 1000 infants) than those surviving. The case fatality associated with any bleeding was 21.3% (95% confidence interval [CI] (19.8-22.8). The estimated case fatality rates associated with early nasal and bruise were 97.6% (95% CI 94.3-99.8) and 79.5% (95% CI 70.5-88.5), respectively. EBF was significantly associated with a 39% increased risk of umbilical bleeding (adjusted odds ratio [OR]= 1.39 (95% CI 1.11-1.73) at 8 days - 3 months of age compared to non-EBF during that same period. Similarly, the adjusted odds ratio for nasal bleeding among deceased infants was 3.01 (95% 1.36-6.65) in 2-7 days of life, reflecting a 3 times increased risk significantly associated with EBF. Maternal PIVKA-II levels measured at the 3rd trimester of pregnancy and 3-months post partum failed to show any significant association with infantile bleeding symptoms.

Conclusion: Reported infantile bleeding, consistent with clinical VKDB, is not uncommon in rural Bangladesh and is associated with extremely high mortality, especially in neonatal life. Our findings also revealed that exclusive breastfeeding may be associated with increased risks of bleeding in these rural Bangladeshi infants. Maternal vitamin K deficiency, measured by plasma PIVKA-II concentration, was not associated with infant bleeding; still, because maternal status may not adequately reflect infant vitamin K status, vitamin K deficiency remains a most likely explanation for bleeding risk in this and other rural populations. Based on the findings, a randomized controlled trial may well be justified to test the efficacy of vitamin K supplementation at birth in preventing vitamin K deficiency bleeding among infants born in rural Bangladesh.

Chapter 1: Introduction and Literature Review

1. Introduction

In 1894, Charles Townsend first described the "Hemorrhagic Disease of the Newborn (HDN)". Thirty-five years later Henric Dam isolated the Vitamin K. For Vitamin K isolation Dam was awarded the Noble Prize, because since then Vitamin K saved lives of thousands of newborns by preventing and treating HDN[1]. Newborn infants encounter a well-established risk of Vitamin K deficiency. Factors contributing to this condition are poor placental transfer, low concentration of plasma clotting factors because of hepatic immaturity, and low Vitamin K content obtained from breast milk. Individually or in combination, these factors increase the risk of bleeding in infants[2].

Vitamin K deficiency bleeding (VKDB) is defined as bleeding due to inadequate activities of Vitamin K dependant coagulation factors (II, VII, IX and X), correctable by Vitamin K replacement[3]. Neonatal bleeding is not necessarily due to Vitamin K deficiency and Vitamin K deficiency often occurs after four weeks of neonatal period[4]. As such, in 1999 the Pediatric/Perinatal Subcommittee of the International Society of Thrombosis and Hemostasis (ISTH) replaced the term "Hemorrhagic Disease of Newborn (HDN)" by "Vitamin K Deficiency Bleeding (VKDB)"[3,4]. Vitamin K deficiency bleeding is largely confined to the first 6 months of life and often occurs without warning, needing emergency treatment. Some infants die and many are left with a permanent mental handicap due to bleeding into the central nervous system[5].

Literature suggests Vitamin K deficiency bleeding as a significant concern in the developed world and might pose as a bigger problem in the developing countries. In neighboring India, Thailand, Vietnam and in other Asian countries e.g. in China and Malaysia the problem was detected at public health significance levels[5-12]. In many developing countries the problem has not yet been studied in its full extent as the potential concern about VKDB is often overshadowed by more common and more visible infectious diseases during infancy.

Interestingly, this bleeding perpetrated by the deficiency of Vitamin K can be effectively prevented by the administration of 0.5-1 mg phylloquinone intramuscularly or 2.0 mg of Vitamin K orally within 6 hours of birth. In the population context, even one oral dose at birth gives considerable protection[1-3,8,11,12]. Thailand is a good example of how an initially very high incidence of VKDB can be reduced by integrating Vitamin K prophylaxis with the national healthcare program[8].

1.1 Major Types of Bleeding in Infants

Over 50 important substances that affect blood coagulation have been found in human blood and tissues. Some are promoting coagulants called pro-coagulants while others are inhibiting coagulants called anti-coagulants. With few exceptions, almost all the blood clotting factors are formed by the liver. Therefore, conditions of the liver such as hepatitis, cirrhosis etc. can depress the clotting system. Premature hepatic system, cholestasis etc. also are accountable for similar conditions in newborn infants.

Excessive bleeding in infancy can result from deficiency of any of the many different blood clotting factors. Six particular types of bleeding tendencies in infancy have been cited extensively in the text[13]:

a. Hemophilia
b. von Willebrand disease
c. Thrombocytopenia
d. Disseminated Intravascular Coagulation (DIC)
e. Necrotizing Enterocolitis (NEC)
f. Vitamin K Deficiency Bleeding (VKDB)

1.1.1 Hemophilia

Coagulation factor VIII and factor IX deficiencies are the most common severe inherited bleeding disorders. Hemophilia is a bleeding tendency that occurs almost exclusively in male infants. In 85% of the cases it is caused by the deficiency of factor VIII. This type of hemophilia is called hemophilia A or classical hemophilia. In another 15% of the cases, the bleeding tendency is caused by deficiency of factor IX and is known as Hemophilia B.

As neither of the factors VIII and IX cross the placenta, bleeding symptoms may present at birth. Neonates with hemophilia may manifest intracranial hemorrhage, although only about 30% of the affected male infants with hemophilia bleed excessively during circumcision. In hemophilic infants bleeding may occur in any area of body but the identifying bleeding of hemophilia is bleeding into the joints. Bleeding could be induced by minor trauma but often bleeding episodes are spontaneous in a target joint, in which bleeding occurs repeatedly[13].

1.1.2 von Willebrand Disease

von Willebrand disease is the most common hereditary bleeding disorder, with some reports suggesting that it is present in 1 to 2% of the general population in western countries[13]. von Willebrand Disease (vWD) is inherited autosomally as a defect of the large component of factor VIII.

1.1.3 Thrombocytopenia

Thrombocytopenia occurs in various fetal and neonatal infections and is responsible for severe spontaneous bleeding. Neonatal thrombocytopenia often occurs following congenital viral infections e.g. rubella, cytomegalovirus and protozoal infections e.g. toxoplasmosis, syphilis etc. Bacterial infections especially gram-negative bacilli also cause thrombocytopenia in infancy. In thrombocytopenic bleeding, bleeding usually occurs from many small venules or capillaries, rather than from the large vessels[13].

1.1.4 Disseminated Intravascular Coagulation

A large number of conditions have been reported to be associated with disseminated intravascular coagulation (DIC) in infancy, including maternal toxemia, abruptio placenta, Group B streptococcal infections, severe respiratory distress syndrome, necrotizing enterocolitis, congenital viral infections (e.g. cytomegalovirus, herpes simplex), septic shock, meningococcemia, erythroblastosis fetalis etc. In disseminated intravascular coagulation, excessive consumption of clotting factors, platelets and anticoagulant proteins occurs, resulting in deficiency of factor VIII, factor V, prothrombin, fibrinogen and platelets. Commonly, the clinical result of this sequence is excessive hemorrhage[13].

1.1.5 Neonatal Necrotizing Enterocolitis

Necrotizing Enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal tract in the newborn period. NEC is characterized by various degrees of mucosal or transmural necrosis of the intestine. The infants with NEC have a variety of signs and symptoms and may have either an insidious or sudden catastrophic onset. The onset of NEC usually occurs in the first 2 weeks but can be as late as 3 months of age in very low birth weight babies. Age of onset is inversely related to gestational age. The first signs are abdominal distension with gastric retention. Bloody stools are seen in 25% of the patients[13].

1.2 Literature on Vitamin K

Vitamin K is a member of the lipid soluble vitamins and encompasses not one vitamin but a group of similar compounds. Vitamin K1 (phylloquinone) is found particularly in green leafy vegetables e.g. spinach, cabbage, cauliflower, legumes, lettuce etc.[14,15]. It is also found in some vegetable oils e.g. soybean oil, canola oil, olive oil etc. Cow milk is also a good source of Vitamin K[14]. Vitamin K2 (a member of menaquinones) is found in lesser amounts in cheese, meat and fermented soy products and is also synthesized by the gut bacteria[16]. In the process of the metabolism by which the body recycles Vitamin K, a carboxylation reaction takes place in which amino acid and glutamic acid are converted to carboxyglutamic acid, thereby making them more attractive to calcium ions. This reaction gives Vitamin K an important role in key physiological functions in human body[16].

1.2.1 Metabolism and Stores of Vitamin K in Human Body

Although Vitamin K is a fat soluble vitamin, the body stores very little of it in liver and spleen[17]. The reserve for Vitamin K is adequate for only one week if there is a complete dietary absence in a healthy person. Vitamin K is mainly absorbed in the terminal ileum, therefore bile salts and normal fat absorption is necessary for the effective uptake of Vitamin K[18]. The adequate intake (AI) for adult males is 120 ug/day, for adult females 90 ug/day and for the newborn (<6 months) 2 ug/day[19].

Bacteria that normally colonize the large intestine synthesize manaquinones (Vitamin K2), which are active forms of Vitamin K. Until recently it was thought that up to 50% of the human Vitamin K requirement might be met by bacterial synthesis. Recent research indicates that the contribution of the bacterial synthesis is much less than previously thought[20].

1.2.2 Level of Vitamin K in Newborns

Infants are born with low levels of Vitamin K due to low transmission of Vitamin K across placenta[14]. The passage of Vitamin K through the placental barrier requires high levels of maternal Vitamin K. When the gradient is not adequate, Vitamin K is deficient at birth[21]. Liver prematurity with prothrombin synthesis and sterile gut in premature neonates account for Vitamin K deficiency in early life[18]. On the other hand, the concentration of Vitamin K in breast milk is generally less than 5ng/ml[22]. Besides that, the intestinal flora of breastfed infants is not efficient in the synthesis of Vitamin K, since lactobacilli do not synthesis Vitamin K[21]. In addition exclusive breastfeeding results in an intestinal flora that is low in Vitamin K producing bacteria[11].

Literature suggests that breast milk can supply only about 20 % of the infant's requirement[4]. However, if mothers consume lots of green vegetables on a daily basis, Vitamin K level can be improved in breast milk[23].

1.3 Vitamin K Dependent Proteins

Vitamin K dependant proteins are present in a wide variety of tissues including plasma, bones etc. and play a major role in key physiological functions[24].

1.3.1 Vitamin K Dependent Pro-coagulation Proteins

The Vitamin K dependent pro-coagulation factors are shown in Table 1.1.

Table 1.1: Coagulation Factors and Associated Bleeding Symptoms[13]

Factors	Bleeding Disorder	Dependent	Severity of Bleeding
I	DIC		Severe in complete absence
II	VKDB	Vitamin K	Usually mild
V	Para hemophilia		Usually mild
VII	VKDB	Vitamin K	Severe when level is low
VIII	Hemophilia A		Severe when level is low
VIII	Von Willebrand's		
IX	Heamophila B & VKDB	Vitamin K	Severe when level is below
X	VKDB	Vitamin K	Moderate to severe when level is low
XI	Hemophilia C		Mild to moderate when level is low
XII			Severe

1.3.2 Vitamin K Dependent Anti-coagulant Proteins

Protein C and S are anticoagulant proteins that provide control and balance in the coagulation cascade. Uncontrolled clotting of blood could be as life threatening as uncontrolled bleeding. Controlled mechanisms are built in the coagulation cascade[20].

1.3.3 Other Vitamin K Dependent Proteins

Besides Vitamin K dependant proteins involved in blood coagulation, researchers have identified other Vitamin K dependent proteins in kidneys (nephrocalcin), bones (osteocalcin) and nerves etc.[25]. Vitamin K is also reported to be required for arterial health (atherocalcin), and some researchers believe that a deficiency can contribute to arteriosclerosis[16]. Another Gla containing protein Gas6 has been found throughout the nervous system, as well as in the heart, lungs, stomach, kidneys and cartilage. Although the exact mechanism of its action has not yet been determined, Gas6 appears to have a cellular growth regulation factor with cell signaling activities. It may play important roles in the developing and ageing of the nervous system[20].

1.3.4 Developmental Anomalies Related to Vitamin K Deficiency in Infants

In infants, some birth defects such as underdevelopment of face, nose, bones and fingers are reported to be linked to Vitamin K deficient status during pregnancy[18,26]. The birth defects that have been reported to be linked with intake of anticonvulsant drugs during gestation, which block Vitamin K, are reported as epicanthal fold, flat nasal bridge, short nose, variety of craniofacial abnormality, neural tube defects, mental retardation, microcephaly, cardiac abnormalities of infants etc.[26].

1.3.5 Blood Coagulation

Vitamin K dependant proteins which are involved in blood coagulations are Prothrombin (factor II), factors VII, IX and X, and protein C, S and Z. Prothrombin and factors VII, IX and X possess pro-coagulant activity whereas proteins C and S act as anticoagulants[27]. Detailed function of protein Z is yet to be known[20].

The binding of calcium ions is required for the activation of the Vitamin K dependant clotting factors in the coagulation cascade. Vitamin K dependant gamma carboxylation of the specific glutamic acid residues in those proteins help them to bind with calcium ions. Factors II, VII, IX and X make up the core of the coagulation cascade[13,20].

1.4 Classification of VKDB Based on Age of Onset[3-5]

1.4.1 Early (<24 hours) VKDB

Early VKDB is defined as bleeding due to Vitamin K deficiency in the first 24 hours of life. This type of bleeding is very rare, and could occur in the first day of life among infants whose mothers took anticonvulsants, antitubercular therapy or Vitamin K antagonist anticoagulants during their pregnancies[4]. It can be fatal due to bleeding at intracranial, intrathoracic, intra abdominal and gastrointestinal sites[28].

1.4.2 Classical (2 to 7 days) VKDB

Classical VKDB is defined as bleeding taking place between 2 days to 7 days of births. It typically presents between 3 and 5 days. A probable cause other than maternal drugs taken during pregnancy, is delayed or inadequate feeding after births. Bleeding is usually from umbilicus, gastrointestinal tract, skin punctures, circumcision, surgical sites and rarely the brain[28,29]. Warning signs such as minimal bleeds, evidence of cholestasis and failure to thrive are often presented[1].

1.4.3 Late (8 days to 6 months) VKDB

The late VKDB is defined as bleeding due to Vitamin K deficiency occurring between 8 days to 6 months of live[3]. The reported peak incidences of late VKDB are between 3 to 8 weeks[8,30,31]. It usually presents as "warning bleeding" e.g. mild bruise, nose bleed or umbilical oozing as the first manifestations followed (sometimes days later) by intracranial haemorrage[3].

Late VKDB occurs almost exclusively in breastfed babies, and often in association with unrecognized liver diseases or malabsorption syndrome[4]. Presenting symptoms of late VKDB could be cuteneous mucosal pallor, hypo activity, discrete jaundice, ecchymoses, nasal bleeding, tense fontanels and irritability[21]. The systems more affected are gastrointestinal tract, urinary system, umbilical cord, respiratory system and nervous system[32].

One study in India reported that the common presenting symptoms of late VKDB were seizures (71%), vomiting (57%), poor feeding (50%), and altered sensorium (36%). Physical examinations revealed pallor in all infants, bulging anterior fontanels in 64% of infants and intracranial bleeding in 93% of infants[6]. Another study in India, reported that the majority of infants (76%) were in the age group of 1 to 3 months. All were term babies being exclusive breastfed and none received Vitamin K at birth. Among them 71% babies presented with intracranial hemorrhage and the commonest sites were intracerebral and multiple intracranial haemorrage[7].

Another study in Turkey, reported the presenting complaints as seizures (91%), drowsiness (82%), poor suckling (64%), fever (46%), pallor (46%), acute diarrhea (27%), irritability and high pitched cry (18%). On examination, tense or bulging fontanel (73%), anisocoria (36%), weak neonatal reflexes (18%), cyanoses (18%) were the most frequent findings[33].

1.4.4 VKDB Classification with Symptoms

Table 1.2: Classification of Vitamin K Deficiency Bleeding Based on Age of Onset and Presenting Symptoms[3,5,13]

	Early VKDB	**Classic VKDB**	**Late VKDB**
Age of onset	0-24 hours	2-7 days	84-6 months
Site of hemorrhage	Cephalhematoma	Gastrointestinal	Intracranial
	Subgaleal	Ear, nose, throat, mucosal	Gastrointestinal
	Intracranial	Intracranial	Cuteneous
	Gastrointestinal	Circumcision	Ear, nose, throat mucosa
	Umbilicus	Cuteneous	Infection sites
	Intra abdominal	Gastrointestinal	Thoracic
		Infection sites	

1.5 Lab Indicators for Bleeding Differentiations between VKDB and other Major Bleeding

In infants who bleed, prolonged Prothrombin time (PT) together with a normal fibrinogen level and platelet count could be almost diagnostic of VKDB; rapid correction of the PT and/or cessation of bleeding after Vitamin K administration are confirmatory of VKDB[4]. PIVKA-II (standing for "protein induced in Vitamin K absence) is also a marker for Vitamin K deficiency. It is plasma protein and is released in absence of Vitamin K. Higher levels of PIVKA-II reflect a lower level of Vitamin K[34].

Table 1.3 Indicators to differentiate DIC and VKDB and Hemophilia[13]

Indicators	DIC	VKDB	Hemophilia
Partial thromboplastin time	P	P	P
Prothrombin time	P	P	N
Thrombin time	P	N	N
Platelet count	L	N	N
Fibrinolytic split products	+	-	-
Fibrinogen	L	N	N
Factor VIII	L	N	L
PIVKA-II	-	H	-

P= Prolonged, N= Normal, L= Low, H=high

1.6 Literature on Incidence and Prevalence of VKDB

It was first shown in 1939 that treatment with Vitamin K could treat symptomatic prothrombin deficiency in the first week of life[22,35,36]. A Swedish study published in Lancet in 1944 showed a five fold reduction in death from hemorrhage within 2 to 8 days after birth if babies were given 1 mg of oral menadione at birth[37]. Until the 1960s, VKDB was considered to be a problem of the first week of life but in 1966 it was first reported from Thailand of another type of VKDB that typically presented between 1 and 2 months of life[38]. In 1977, Bhanchet and collegues reported a high incidence of VKDB in breastfed infants (98%) and high incidence of intracranial bleeding (63%) among Thai infants[39].

Another paper published in Lancet (1983) reported a resurgence of the VKDB in the United Kingdom not just in the first week of life but also in older babies [40]. These babies were otherwise healthy except there was fatal intracranial bleeding during 2 to 10 weeks after birth. In the countries where circumcision is a ritual reported excessive bleeding and presentation was much the same as in countries where prophylaxis was not given[9,29,41].

High incidence rates of classical VKDB were reported in Southeast Asia. A review in Thailand cited incidence rates of 0.9 and 0.5 per 1000 births in two longitudinal community based studies. In this review, VKDB was found exclusively in breastfed infants (92%) and among the infants who were not given Vitamin K prophylaxis at birth (90%). The reporting of intracranial hemorrhage were strikingly high (82%) and the fatality rate was 24%[8]. Studies conducted in Malaysia in 1987 and 1988 reported the incidence of classical VKDB as 0.3 per 1000 births[9].

Chinese literature review by Zhang et al. revealed as like other countries, nearly all the infants had intracranial hemorrhage (92%) and had been breastfed (89%). The reported peak incidence was within 4 to 8 weeks (79%) and the male/female ratio was 2.6[5]. Another Chinese study reported overall incidence of VKDB at 3.3 in 1000 live births, higher in rural areas (4.9 in 1000 life births) than in urban areas (1.2 in 1000 life births). Most of the bleeding were among the breastfed infants (95.6%) and incidence of VKDB in premature babies (22.5 in 1000 life births) was higher than full term (2.9 in 1000 life births)[10]. A study conducted in Vietnam reported incidence of late VKDB at 1.4 in 1000 live births in the rural areas[12]. The incidence rates of late VKDB in infants with no history of Vitamin K prophylaxis varied from 0.04 to 0.7 per 1000 births in other Asian and European studies[21].

1.7 Literature on Determinants of VKDB

1.7.1 Risk factors

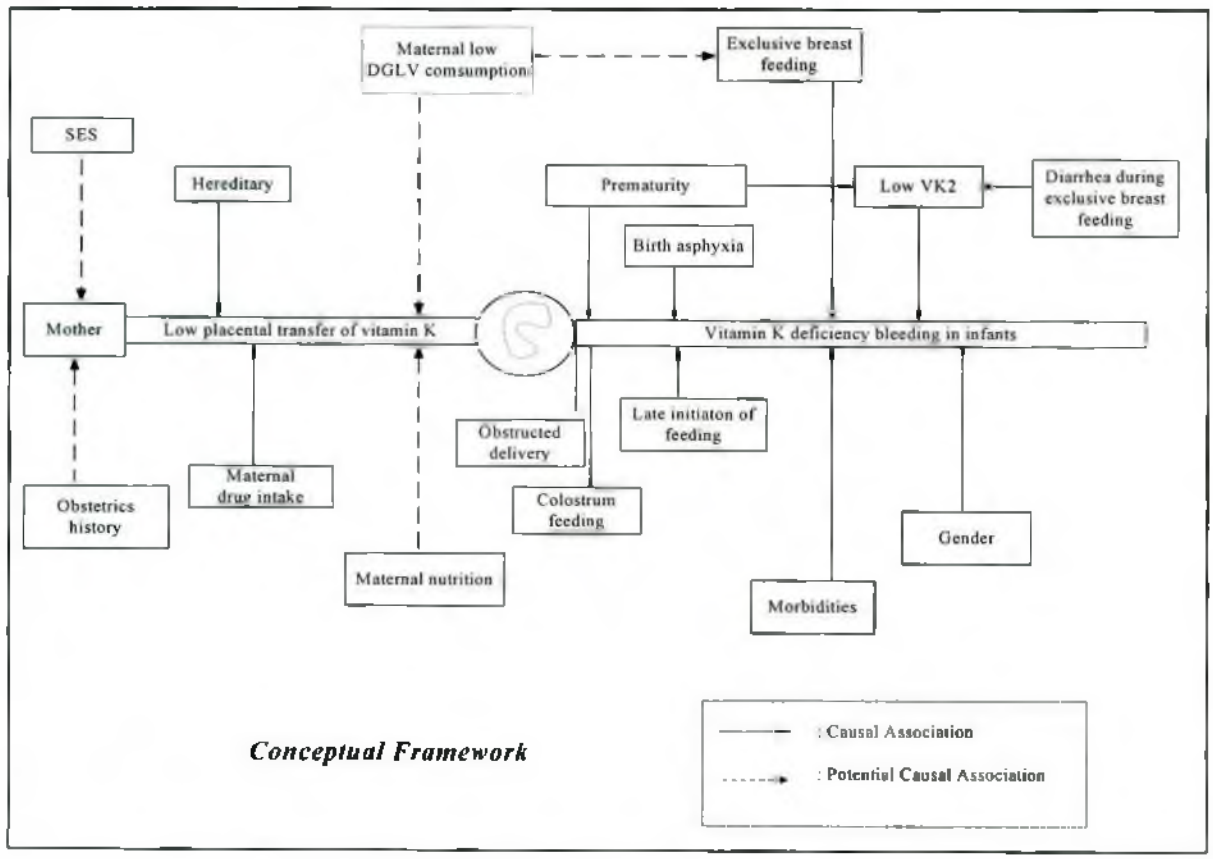
- Maternal drug intake during pregnancy (e.g. anticonvulsants, anti-tubercular etc.), premature babies, asphyxia at birth, breastfeeding and sickness within 2 weeks of birth[10].
- Exclusive Breastfeeding and male child[3-5,11]
- Diarrhea, male baby, cystic fibrosis, biliary atresia, hepatitis, maternal exposure to warfarin and other anticonvulsants drugs[21].
- Diarrhea particularly in exclusively breastfed infants and obstructed labor[23].
- Premature infants, infants exposed to perinatal asphyxia and breastfeeding[42].
- Delay in initiation of breastfeeding and inadequate feeding[42].

1.7.2 Protective Factors

- Supplementation of Vitamin K after birth[1,3,8,11,12] and colostrum feeding[5]

1.7.3 Conceptual Framework

Fig 1.1 Conceptual Framework



1.8 Literature on Prophylaxis of VKDB

This life threatening condition of VKDB can be effectively prevented by the administration of Vitamin K, if infants are given 0.5-1 mg phylloquinone intramuscularly or 2.0 mg orally within 6 hours of birth. In the population context, even one oral dose at birth has been reported to give considerable protection[2,12]. Thailand is a good example where initially very high incidence rates of VKDB was reduced by the integration of Vitamin K prophylaxis in the national healthcare program[8].

The results of two studies on Vitamin K levels in premature infants suggested that the standard initial dose of Vitamin K1 for full term infants (1.0 mg) may be too high for premature infants. These findings have led to suggest the use of an initial Vitamin K1 of 0.3 mg/kg for infants with birth weights less than 1,000 g and an initial dose of 0.5 mg for other premature infants[20].

The American Academy of Pediatrics recommends that every newborn should receive 0.5 to 1 mg of Vitamin K intramuscularly at birth. Oral prophylaxis in a 2 mg dose at birth, between the 1st and 2nd week, and in the 4th week is an alternative. When the newborn develops diarrhea and on exclusive breastfeeding, prophylaxis must be repeated[21].

In the early 1990s Golding el al. published two studies suggesting link between intramuscular Vitamin K (usually Konakion) given to babies for the prevention of Vitamin K deficiency bleeding and subsequent childhood cancer[43,44]. However, subsequent studies with the same objectives found no risk or risks much smaller than those reported by Golding[45-49]. Similarly, Ross and Davis found no evidence of an association between parenteral Vitamin K prophylaxis and cancer in childhood. In this review, ten case-control studies were identified; of which 7 found no relation and 3 found only a weak relationship of neonatal administration of intramuscular or intravenous Vitamin K with a risk of solid childhood tumors or leukemia[50]. After Golding's results, the British Pediatrics Association recommended that the use of intramuscular Vitamin K should be confined to high risk babies only and the rest should receive oral doses[51]. Following the controversy of the possible link between intramuscular Vitamin K with childhood cancer, there has been a notable shift towards oral prophylaxis to prevent VKDB in infants[5].

Chapter 2. Rational and Objectives

2.1 Rationale

Innumerable studies suggest that bleeding due to Vitamin K deficiency is a significant concern in the developed world and could be a much larger problem in the developing countries[5,11]. In many developing countries like Bangladesh this problem has not yet been studied. The concern of VKDB could be unnoticed in the developing countries as the health authorities are primarily concerned with more common and visible infectious diseases and malnutrition. Probably due to this reason, the magnitude and extent of infantile bleeding disorders in Bangladesh are yet not known. In neighboring India, Thailand, Vietnam, China and Malaysia the problem of Vitamin K deficiency bleeding are reported to be at public health significance levels[5-10,12].

In Bangladesh, around 36% to 50% of infants are born with low birth weight[52,53] and around 40% of infants with prematurity[54]. Infant mortality and neonatal mortality rates are 54 and 36 per 1000 live births[53] respectively in Bangladesh. Yet, the contribution of bleeding disorders and those that could be due to Vitamin K deficiency to neonatal and infant mortality are unknown. Based on available literature, premature babies may have an immature or under developed gut and hepatobiliary system, which could predispose them to a Vitamin K deficiency status[2,18]. Mothers are undernourished[55] and breastfeeding is nearly universal in Bangladesh. Following the nationwide campaign for exclusive breastfeeding the practice of exclusive breastfeeding is also on rise[53,55-57]. On the other hand, the initiation of breastfeeding is often delayed, which is a known risk factor[42]. Similarly exclusive breast feeding is the most often identified risk factor[3-5,10,11,23,42] for Vitamin K deficiency bleeding.

In addition to the prevailing risk factors, more than 90% of the deliveries in rural Bangladesh are conducted at home and attended by untrained providers[57]. This adds to the problem of identifying any emergency situation like Vitamin K deficiency bleeding in the neonatal and later infancy periods.

Due to ignorance of parents and community health workers, warning signs of bleeding e.g. nasal bleeding, bruising etc. which are potential indications of Vitamin K deficiency bleeding often go unnoticed in the community settings. The truth is that the burden of such ignorance is hindering the fact of the true extent of the problem and thereby there are no measures to intervene this preventable cause of infant morbidity and mortality in rural Bangladesh.

This condition can effectively be easily prevented by the administration of Vitamin K by 0.5-1 mg phylloquinone intramuscularly or 2.0 mg orally within 6 hours of birth. In the community context, even one oral dose at birth has been reported to give considerable protection[2,12]. Thailand was a good example of how an initially very high incidence of VKDB was reduced by the integration of Vitamin K prophylaxis in the national healthcare program[8]. Considering the importance, identified gap of knowledge and prevailing conditions for occurring Vitamin K deficiency bleeding among infants, urgency was felt to study the magnitude of this preventable problem in rural Bangladesh.

2.2 Research Questions

1. What were the incidence rates and severity of bleeding symptoms among infants born in rural Bangladesh?
2. What were the morbidities associated with bleeding symptoms among infants born in rural Bangladesh?
3. What maternal and infant risk factors were associated with bleeding symptoms among infants born in rural Bangladesh?
4. Whether there was any association between reported bleeding symptoms of infants and maternal PIVKA-II levels at third trimester of pregnancy and at 3 months post partum period?

2.3 Ultimate Objective

The study would estimate the incidence, severity and determine the risk factors associated with bleeding symptoms to define the problem and therefore help design future studies aimed towards its prevention.

2.4 General Objective

To estimate the incidence rates, severity and determinants of bleeding symptoms among infants born in rural Bangladesh.

2.5 Specific Objectives

The specific objectives of this study were to estimate the followings:

1. To determine incidence rates of bleeding symptoms among infants born in rural Bangladesh.
2. To determine case fatality rates (as to measure severity) of bleeding symptoms among infants born in rural Bangladesh.
3. To describe the morbidities that the infants had during their first 6 months of live in rural Bangladesh.
4. To determine what maternal and infant factors are associated with bleeding symptoms among infants born in rural Bangladesh.
5. To determine the association between maternal PIVKA-II level and infantile bleeding among infants in rural Bangladesh.

2.6 Hypotheses

The analyses were aimed to test the following hypotheses:

1. Prematurity was associated with increased risk of bleeding among infants.
2. Risk of bleeding was more in the male infants than the females.
3. Maternal multi-parity was associated with increased risk for infants' bleeding.
4. Exclusive breastfeeding was associated with increased risk of bleeding.
5. Morbidites are associated with increased risk of bleeding.
6. Twin babies were associated with increased risk of bleeding.
7. There were no associations between maternal 3rd trimester and 3 month post partum PIVKA-II levels and bleeding symptoms of infants.

Chapter 3. Methodology

3.1 Study Population

This study was conducted in the rural areas of Rangpur where a large epidemiological study was already in place under the name of JiVitA Project (Appendix I). The JiVitA Project[58] is a maternal, child health and nutrition research project, implemented by the Johns Hopkins University Bloomberg School of Public Health (JHU), Maryland, USA. This Research Project is a component of the USAID and Bangladesh Health and Population Program (UBHPP) of the Ministry of Health and Family Welfare, Government of Bangladesh.

The project working area covers a population of about 650,000 in 19 unions covering a rural area of 650 km^2 in Gaibandha and Rangpur districts. A joint team of JHU scientists and senior Bangladeshi researchers have developed this area into a population research site. With a total staff of over 850 (95% of whom are local women), JiVitA has GIS-mapping of over 160,000 households and has already conducted two trials to evaluate the impact of maternal and neonatal Vitamin A supplementation in reducing mortality and improving health of mothers and newborn infants, respectively.

3.2 JiVitA Trial Context

As the present study has utilized the set up and population of the JiVitA Project, for a better understanding of the current study, it would be pertinent to discuss the JiVitA Project in some details. The JiVitA Project has built its research capabilities since beginning operations in 1998. Two large studies have recently been completed.

The first one was a large-scale, randomized, double-masked community trial to extend previous findings from Nepal that a weekly, low-dose antenatal-to-postnatal supplementation of Vitamin A or beta-carotene can reduce maternal mortality and exert a modest reduction in infant mortality[60]. The Nepal study found a reduction of 44% maternal mortality. The second, concurrent trial was implemented to evaluate the effects of newborn Vitamin A supplementation on infant mortality to extend findings from a recent study in India[61] where Vitamin A supplementation at birth reduced infant mortality by ~20%. As of October 2006, over 65,000 pregnancies have been identified and enrolled by JiVitA field team. In addition, over 15,000 newborns have been enrolled and visited in the home by JiVitA data collection team right after birth.

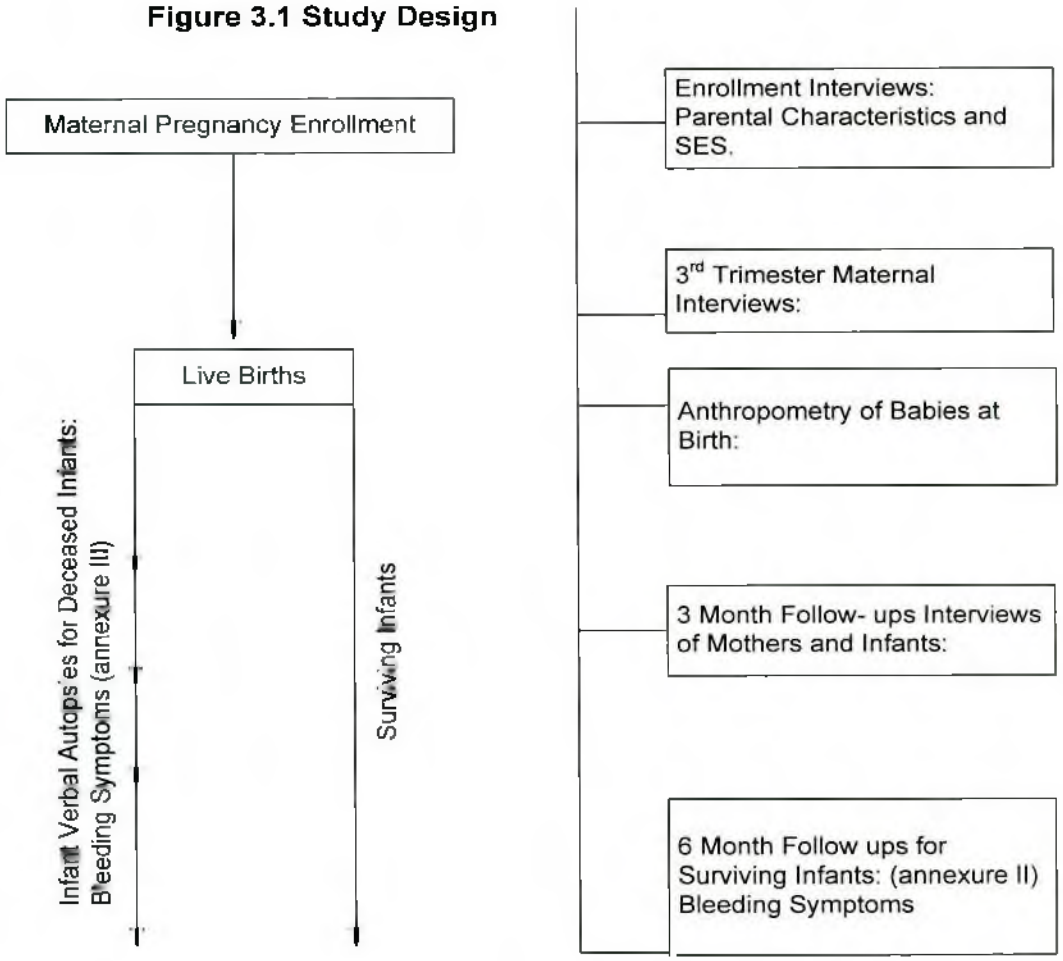
Within the two current trials there were several smaller studies, including those examining effects of adolescent pregnancy on maternal growth and birth outcomes, studies on the epidemiology of bacterial vaginosis and infant nasopharyngeal colonization with Haemophilus influenza B and Streptococcus pneumoniae (causal pathogens of acute respiratory infections), evaluations of body composition methods and change during pregnancy in relation to pregnancy and the index study "an epidemiologic study of Vitamin K deficiency bleeding among infants".

JiVitA has also several very successful collaborative research projects with the Institute for Nutrition and Food Sciences, Dhaka University, the Institute for Child and Mother Health, Dhaka, Shishu Hospital, Dhaka, and with the Bangladesh Atomic Energy Commission (BAEC) / International Atomic Energy Commission (IAEA).

3.3 Study Design

The study protocol followed a non-concurrent prospective design (retrospective cohort) to collect data related to exposures and outcomes of interest on infants who were participating in the JiVitA-1 trial, carried out in Gaibandha and southern Rangpur districts. Live born babies born to mothers enrolled in the JiVitA-1 trial from May 2001 to October 2006 comprised the cohort of eligible infants. Histories of infantile bleeding symptoms (bleeding from the nose, umbilicus, rectum, bruise on the body and bulging fontanel) that may have been observed throughout the first six months of life were collected from mothers at 6 mo of age (Appendix-II) or during verbal autopsy interviews (Appendix -III), typically conducted within one month of an infant death <6 months of age. Data for two cohorts, of 26,705 surviving and 3,139 deceased infants, were analyzed for estimating incidence rates, case fatality rates and odds ratios for infant bleeding, adjusted for potential confounders.

Figure 3.1 Study Design



3.4 Study Subjects

Live born babies of enrolled mothers in JiVitA project from May 2001 to October 2006 were assembled to construct the cohort. Vital status data were available for 29,844 live born infants. The total number of infants who died in the first six months of life was 3,139, which represents the full analytic cohort of infants who were deceased by six months of age. Thus, the number of infants who survived up to 6 months of age was 26,705, which represented the full cohort of surviving infants in this analysis.

3.5 Selection Criteria

3.5.1 Inclusion Criteria

According to the literature most of the vitamin K deficiency bleeding occurs within 6 months of age[3]. Based on that the inclusion criteria were set for the study infants. For the surviving cohort the inclusion criterion was; babies aged 6 months and interviews completed for their 6 months follow-up visits. For cohort of deceased infants the inclusion criterion was; babies died within 6 months of age and their verbal autopsies completed.

3.5.2 Exclusion Criteria

Dark stools for first two days of life were excluded from the analysis for both surviving and deceased infants to remove the possibility of meconium at birth being reported as dark stools.

3.6 Ethical Clearance

The JiVitA trial[58] in which the data collection of the index study was nested had ethical clearance from Bangladesh Medical Research Council (BMRC) and Committee on Human Research at the Johns Hopkins University, Bloomberg School of Public Health, USA.

3.7 Sample Size and Power Calculation

Literature suggests prematurity at birth[10,23,42] and exclusive breastfeeding[3,4,10,23,42] as risk factors for Vitamin K deficiency bleeding among infants. The sample size and power were calculated based on the assumption of the effects of prematurity and exclusive breast feeding on bleeding symptoms. Two sample test of proportions were assumed to test the differences in incidence of bleeding symptoms between those premature vs. mature and exclusively breastfed vs. not exclusively breastfed.

Taking $\alpha = 0.05$ and calculation of the sample size n, required for each group was estimated using the formula:

$$n = \frac{[Z_{1-\alpha}\sqrt{2p(1-p)} + Z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}]^2}{(p_2 - p_1)^2}$$

where $p = \frac{p1 + p2}{2}$ and p_1 and p_2 are the expected proportions of infants with bleeding symptoms in the two groups[62]. Table 3.1 shows the required sample size in each group for different scenarios of p_1 and p_2, and for β taken as 0.8 or 0.9. The calculations assumed equal sample sizes in both groups.

Table 3.1: Required sample size in each group of bleeding status, assuming p1 and p2, to detect a difference between the two proportions at $\alpha = 0.05$ with a power of $\beta = .8$ and .9 The odds ratio (from group 1 to group 2) that can be detected with the n in each cell are given in its subscript.

	P2 (proportion of bleeding symptoms in premature infants/exclusive breastfed infants)								
	0.06	0.08	0.10	0.12	0.14	0.16	0.18	0.20	0.30
p1 (beta = .8)									
0.06		$2011_{(1.30)}$	$568_{(1.60)}$	$280_{(1.87)}$	$173_{(2.13)}$	$120_{(2.38)}$	$90_{(2.62)}$	$70_{(2.84)}$	$31_{(3.72)}$
0.08	$2011_{(0.77)}$		$2531_{(1.22)}$	$694_{(1.43)}$	$335_{(1.64)}$	$203_{(1.83)}$	$139_{(2.01)}$	$102_{(2.17)}$	$38_{(2.85)}$
0.10	$568_{(0.63)}$	$2531_{(0.82)}$		**$3025_{(1.17)}$**	$815_{(1.34)}$	$387_{(1.49)}$	$232_{(1.64)}$	$157_{(1.78)}$	$48_{(2.33)}$
0.12	$280_{(0.53)}$	$694_{(0.70)}$	**$3025_{(0.85)}$**		$3495_{(1.14)}$	$929_{(1.27)}$	$437_{(1.40)}$	$259_{(1.52)}$	$62_{(1.99)}$
0.14	$173_{(0.47)}$	$335_{(0.61)}$	$815_{(0.75)}$	$3495_{(0.88)}$		$3940_{(1.12)}$	$1038_{(1.23)}$	$484_{(1.33)}$	$82_{(1.74)}$
0.16	$120_{(0.42)}$	$203_{(0.55)}$	$387_{(0.67)}$	$929_{(0.79)}$	$3940_{(0.90)}$		$4361_{(1.10)}$	$1140_{(1.19)}$	$111_{(1.56)}$
0.18	$90_{(0.38)}$	$139_{(0.50)}$	$232_{(0.61)}$	$437_{(0.72)}$	$1038_{(0.82)}$	$4361_{(0.91)}$		$4756_{(1.08)}$	$156_{(1.42)}$
0.20	$70_{(0.35)}$	$102_{(0.46)}$	$157_{(0.56)}$	$259_{(0.66)}$	$484_{(0.75)}$	$1140_{(0.84)}$	$4756_{(0.92)}$		$231_{(1.31)}$
0.30	$31_{(0.27)}$	$38_{(0.35)}$	$48_{(0.43)}$	$62_{(0.50)}$	$82_{(0.57)}$	$111_{(0.64)}$	$156_{(0.70)}$	$231_{(0.76)}$	
p1 (beta = .9)									
0.06		$2786_{(1.30)}$	$786_{(1.60)}$	$388_{(1.87)}$	$239_{(2.13)}$	$166_{(2.38)}$	$124_{(2.62)}$	$97_{(2.84)}$	$42_{(3.72)}$
0.08	$2786_{(0.77)}$		$3505_{(1.22)}$	$962_{(1.43)}$	$464_{(1.64)}$	$281_{(1.83)}$	$192_{(2.01)}$	$141_{(2.17)}$	$53_{(2.85)}$
0.10	$786_{(0.63)}$	$3505_{(0.82)}$		**$4190_{(1.17)}$**	$1129_{(1.34)}$	$536_{(1.49)}$	$320_{(1.64)}$	$216_{(1.78)}$	$67_{(2.33)}$
0.12	$388_{(0.53)}$	$962_{(0.70)}$	**$4190_{(0.85)}$**		$4841_{(1.14)}$	$1287_{(1.27)}$	$605_{(1.40)}$	$358_{(1.52)}$	$86_{(1.99)}$
0.14	$239_{(0.47)}$	$464_{(0.61)}$	$1129_{(0.75)}$	$4841_{(0.88)}$		$5458_{(1.12)}$	$1437_{(1.23)}$	$669_{(1.33)}$	$113_{(1.74)}$
0.16	$166_{(0.42)}$	$281_{(0.55)}$	$536_{(0.67)}$	$1287_{(0.79)}$	$5458_{(0.90)}$		$6040_{(1.10)}$	$1578_{(1.19)}$	$153_{(1.56)}$
0.18	$124_{(0.38)}$	$192_{(0.50)}$	$320_{(0.61)}$	$605_{(0.72)}$	$1437_{(0.82)}$	$6040_{(0.91)}$		$6588_{(1.08)}$	$215_{(1.42)}$
0.20	$97_{(0.35)}$	$141_{(0.46)}$	$216_{(0.56)}$	$358_{(0.66)}$	$669_{(0.75)}$	$1578_{(0.84)}$	$6588_{(0.92)}$		$319_{(1.31)}$
0.30	$42_{(0.27)}$	$53_{(0.35)}$	$67_{(0.43)}$	$86_{(0.50)}$	$113_{(0.57)}$	$153_{(0.64)}$	$215_{(0.70)}$	$319_{(0.76)}$	

From table 3.1, if it is assumed that the incidence of bleeding in premature infants is at 12% and in mature infants at 10%, at least a total of 6,050 infants (3,025 for infants who had bleeding and 3,025 for infants who did not have bleeding) would be needed (using 80% power to detect the difference). Similarly, if 90% power is used, at least 8,380 (4190x2) infants would be needed.

3.8 Data Collection Methods

For collection of maternal data, trained female interviewers interviewed mothers at pregnancy enrolments, at 3rd trimester of pregnancies and at 3 month post partum follow up visits. At enrollment interviews, maternal characteristics, past obstetric histories and socioeconomic status etc. were collected. Delivery data were collected at 3 month post partum interviews. In a sub-sample of mothers, blood samples were drawn at 3rd trimester of pregnancy and at 3 months post partum visits. Mothers were sampled for those infants who had bleeding symptoms within 6 months of age and drawn a matched sample of mothers whose infants did not have bleeding, infants being matched for their gestational age.

For infants' data, trained interviewers visited newborns at births and interviewed mothers at 3 months and at 6 months follow ups of their surviving infants. Similarly trained female interviewers conducted verbal autopsies to collect detailed data on the deceased infants from their parents. In JiVitA trial, live births were reported through a systematic community based birth notification system. During 3rd trimester of pregnancy the enrolled mothers were given address cards of the local field workers and family members were requested to inform them as soon as the births took place.

At birth, weights, head circumferences, chest circumferences, mid upper arm circumferences and lengths were measured. As the infants' trial was started later (in 2003), anthropometry was available for fewer infants than total live births of the main trial. Data on breastfeeding, complementary feeding, infants' morbidities were collected at birth, at 3 months, and at 6 months visits for cohort of surviving infants and for the cohort of deceased infants during verbal autopsies.

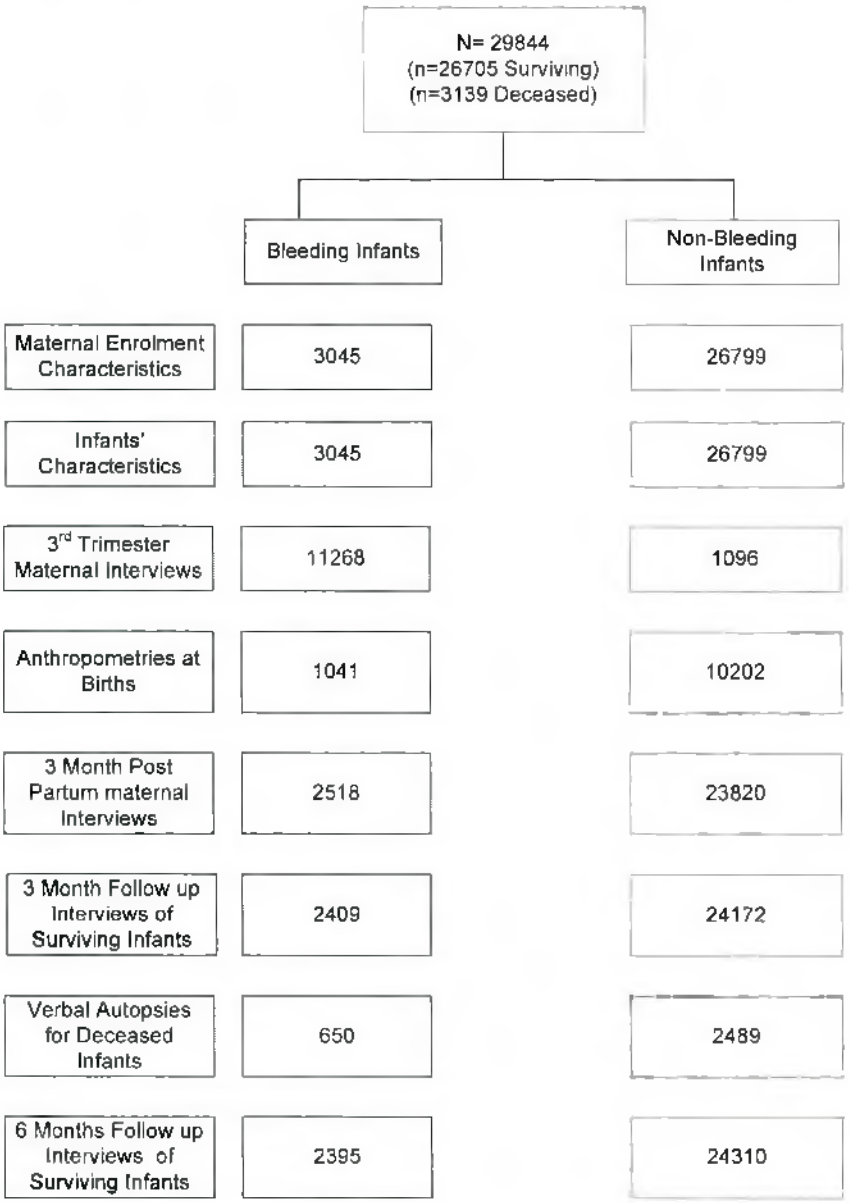
3.8.1 Data on Bleeding Symptoms for Surviving Infants

For surviving infants, nasal bleeding, bruising, umbilical bleeding, red blood in stool (fresh intestinal bleeding), dark stools, excessive bleeding during circumcision and bulging fontanel were asked as 'questions/symptoms on bleeding' during the 6 months follow up visits (Appendix- II). Parents were asked to report the listed bleeding symptoms with the time of onset of first episodes. The six month follow up interviews for surviving infants remained valid up to their 28 weeks of age.

3.8.2 Data on Bleeding Symptoms for Deceased Infants

For deceased infants, parents were asked for nasal bleeding, bruising, umbilical bleeding, red blood in stool (fresh intestinal bleeding), dark stools, excessive bleeding during circumcision and bulging fontanel during the deceased infants' verbal autopsies (Appendix- III). Parents were asked to report the listed bleeding symptoms with the time of onset of first episodes. Verbal autopsies were scheduled one week after death of infants and most of the verbal autopsies were completed within 1 month of death.

Figure 3.2 Data Collection Flow Diagram



3.9 Data Quality Control

The interviewers were trained on each of the bleeding questions separately. They were trained on the operational definitions (Appendix-VI) and on standardized interview techniques e.g. rapport building, probing, coding, cross checking etc.

Repeated field testing of the questions were done to ensure that the rural mothers understood the questions asked. Local dialects were incorporated in the questionnaires for the interviewers. All the completed questionnaires were checked for consistency and completeness before closing the interviews.

Completed forms were cross-checked in peer review sessions of female interviewers at the field levels before submitting for data entry. At the data entry center, customized data entry programs were used. Data errors were checked within one week of data collection at data management center and errors were sent back to field for cross-checking. The turn around period of the correction of errors to data management center ranged from 1-2 weeks.

3.10 Analytical Strategy

Data cleaning, labeling and analysis were performed using STATA Statistical Soft-ware, version 9.0[63]

3.10.1 Characterization of Parents and Infants

Any bleeding symptom was constructed considering parental reporting of all bleeding symptoms that their infants had for both of the cohorts. Bleeding symptoms were categorized based on the time of onset of bleeding as early onset (< 24 hours), classical onset (2 days to 7 days) and late onset (8 days to 6 months)[3]. Data were analyzed based on the time of onset of bleeding for individual bleeding symptoms e.g. nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding and combinations of bleeding symptoms such as nasal bleeding with either (a) bruising, or (b) bulging fontal, or nasal bleeding with either (c) bruising or umbilical bleeding.

Symptoms were combined as such to evaluate the potential that they could confer different levels of risk of mortality for infants. Stratified analysis were also been done based on the time of onset of bleeding for individual bleeding and for any combination of bleeding status with other explanatory variables e.g. breastfeeding, infantile characteristics, morbidities etc. separately for the both cohorts of surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders.

Bi-variate analyses were performed with Pearsons chi-square test for the differentiations of any bleeding status of infants with the categories of parental and infantile characteristics. Missing values were excluded from the analyses. Associations of bleeding status with parental and infantile characteristics were also tested by 2x2 tables. T-test and non-parametric ranksum tests were used to test the association of bleeding symptoms by comparing the mean and median differences of parental and infantile characteristics, respectively. For all tests used in these analyses, statistical significances were set at 0.05 levels.

3.10.2 Incidence Rates and Relative Risks

Incidence rates were calculated on the basis of reported bleeding events (numerator) among infants who were alive at the outset of a specified age interval. Thus, among surviving infants, the denominator for the total and age-specific incidence rates was 26,705 as this number of infants survived to six months of age.

However, the denominator for the cohort of infants who died by six months of age has been recalculated to reflect the number alive at birth, after the first day of life and after the seventh day of life, as they had to have been alive within the interval to be at risk of having a bleeding episode at that age. Thus, the denominators for infants in the deceased cohort were 3139, 1936 and 1198 for incidence rates calculated for this cohort during the early (< 24 hours), classic (2 to 7 days of age) and late (8 days to 6 months of age) periods, respectively. Relative risks (RR) were also calculated along with their 95% CI for individual and combined bleeding symptoms for early, classic and late onset.

3.10.3 Mean and Median Time to Death from Bleeding Interval

The mean, median, inter-quartile range, standard deviation and 95% CI of the mean time to death from the interval at which a bleeding symptom was reported for the cohort of deceased infants was also analyzed.

3.10.4 Case Fatality Rates

Formula used for calculating Case Fatality Rates:

(number of bleeding symptoms in deceased)/(number of bleeding symptoms in deceased + number of bleeding symptoms in survived) x 100

Case fatality rates with their 95% confidence intervals were calculated for individual and combination of bleeding symptoms, based on the time of onset as early onset (< 24 hours), classical (2 days to 7 days) and late (8 days to 6 months).

3.10.4 Determinants Analysis

Crude odds ratios with 95% confidence intervals were calculated for the potential determinants e.g. colostrum feeding, EBF, gender, maturity at birth, numbers of siblings, birth weights, infants' morbidities (cough/cold, high fever, breathing difficulties, diarrhoea, dysentery), maternal parity and religion for individual and combination of bleeding symptoms based on time of onset of bleeding for surviving and deceased infants separately. Onset of bleeding was classified as < 24 hours, 2 to 7 days, 8 days to 3 months and 3 months to 6 months of age. Adjusted odds ratios with 95% confidence intervals were calculated using logistic regression based on the time of onset of individual and combination of bleeding symptoms separately for both the cohort of surviving and deceased infants. To asses the independent effect of any determinant (e.g. gender) on the bleeding symptoms the odds ratios were adjusted for that determinant (in this case gender) for the rest of the determinants list e.g. maturity at birth, number of siblings, colostrum feeding, EBF, infants' morbidities (cough, breathing difficulties, high fever, diarrhoea, dysentery), maternal age, maternal parity, obstructed delivery and religion.

3.10.5 PIVKA-II Analysis

Maternal 3rd trimester and 3 month postpartum PIVKA-II levels analysis were done at Johns Hopkins University using a commercial enzyme-linked immunoassay (ELISA) kit of PIVKA-II[64]. PIVKA-II is a plasma protein and is released in absence of Vitamin K, and stands for "Protein Induced in Vitamin K Absence". Higher levels of PIVKA-II reflect lower levels of Vitamin K. The commonly reported cut-off for PIVKA-II for adult females is 2 ng/ml[34].

As the number of individual bleeding symptoms were very small for different age of onset intervals for which PIVKA-II samples were drawn, it was not possible to evaluate protein concentration differences by individual bleeding symptoms but possible to evaluate differences for any bleeding symptoms. For the same reason there was insufficient power to analyze PIVKA-II levels separately across cohorts of surviving and deceased infants. Maternal plasma protein concentrations were also assessed by their dietary intake during the 3rd trimester of pregnancy and at 3 months postpartum periods, specifically their reported frequencies of intake of dark green leafy vegetables (DGLV). Dietary intakes were also evaluated in the sub sample of mothers to look for any association between their DGLV consumption and their infants' bleeding, irrespective of maternal plasma PIVKA-II levels.

Association between any bleeding status and maternal PIVKA-II levels were analyzed by comparing the means and proportions, and for these analyses ttests and Pearson chi-square tests were used, respectively. The cut off for maternal PIVKA-II level was set at 2ng/ml for the proportion distribution. For this analysis time of onset of bleeding was classified as < 24 hours, 2 days to 7 days, 8 days to 3 months and 3 months to 6 months of age. Association between any bleeding status of infants and maternal consumption of dark green leafy vegetables (DGLV) were analyzed by Persons chi-square tests and comparing the medians and standard deviations using non-parametric ranksum tests. Association between maternal PIVKA-II levels and maternal consumption of dark green leafy vegetables (DGLV) were analyzed by 2x2 tables and comparing the medians and standard deviations using non-parametric ranksum tests.

Chapter 4. Parental Characteristics

In this chapter, the bleeding status of infants were analyzed with parental characteristics e.g. maternal age, maternal parity, religion, education, occupation, maternal MUAC and maternal DGLV consumption during 3rd trimester of pregnancy and 3-month post partum period. The bleeding status of infants for maternal delivery characteristics e.g. place of delivery, birth attendants and type of deliveries were also looked into.

4.1 Distribution of Study Infants

In the cohort there were 29,844 live born infants at the outset. Among 26,705 infants who survived up to 6 months of age, 2395 (9.0%) were reported by their parents to have had any bleeding symptoms at any time up to that age (Table 4.1). In contrast, among the 3139 infants who died at 6 months of age, 650 (20.7%) were reported by parents to have had any symptoms of bleeding prior to death. Thus, of all 29,844 infants in the study, including both survivors and infants who later died by age six months, parents reported symptoms of bleeding in 3045 or 10.2% of all study infants.

Table 4.1. Distribution of bleeding status of infants by their survival status

Survival Status	Infants who had any bleeding	%	Infants who did not have bleeding	%	Total	%
Surviving	2395	78.7	24310	90.7	26705	89.5
(%)	(8.9)		(91.0)		(100)	
Deceased	650	21.3	2489	9.3	3139	10.5
(%)	(20.7)		(79.3)		(100)	
Total	3045	100	26799	100	29844	100
(%)	(10.2)		(89.8)		(100)	
Pearson Chi^2 (1) =422.4622					*P-value<0.0001*	

4.2 Maternal Age

When maternal age distributions were analyzed for infants who had bleeding and who did not have bleeding, similar percentages were found for all categories of maternal age for both types of infants (Table 4.2). The mean maternal age of infants who had bleeding was 22.4 ± 6.1 years and the corresponding mean of maternal age of the infants who did not have bleeding was 21.9 ± 5.7 years, the difference being statistically significant (p = < 0.001).

Table 4.2: Distribution of bleeding status of infants by their maternal age

Age in Years	**Infants who had bleeding** n= 3045		**Infants who did not have bleeding** n= 26799	
	No.	%	No.	%
10-14	120	3.9	1150	4.3
15-19	1039	34.1	9813	36.6
20-24	894	29.4	8050	30.0
25-29	562	18.5	4693	17.5
30-34	284	9.3	2145	8.0
35+	141	4.6	901	3.4
Don't Know	5	0.2	47	0.2
Pearsons Chi^2(6) =25.7761				*p-value <0.0001*
Mean	22.41		21.94	
SD ±	6.1		5.7	
T-test	*T=-4.2549*			*p-value < 0.001*

4.3 Maternal Parity

When bleeding status of infants were analyzed by the categories of maternal parity, comparatively less (36.1 % vs. 39.7%) percentages of infants who had bleeding were found among the nulliparaous mothers compared to that of infants who did not have bleeding (Table 4.3). The percentage distributions of both types of infants were similar (43.3 % vs. 43.0%) for parity 1-2 category. Mean number of maternal parity was 1.42 ± 1.57 for infants who had bleeding and 1.27 ± 1.48 for mothers of infants who did not have bleeding. The median number of maternal parity was 1 for both types of infants.

Table 4.3: Distribution of bleeding status of infants by maternal parity

Parity	**Infants who had bleeding** n=3039		**Infants who did not have bleeding** n=26769	
	No.	%	No.	%
0	1098	36.1	10625	39.7
1-2	1320	43.4	11520	43.0
3-4	483	15.9	3559	13.3
5+	137	4.5	1060	4.0
Don't know	1	0.03	5	0.02
Pearsons Chi^2 (4) =24.805				*p-value <0.001*
Mean	1.42		1.27	
Median	1.0		1.0	
SD±	1.57		1.48	
Ranksum test Z=5.738				*p-value <0.001*

4.4 Religion

Majority of the infants in either group were borne of Muslim mothers (Table 4.4). Comparatively less infants who had bleeding (6.9%) than infants who did have bleeding (8.1%) got reported among the Hindu mothers (p = <0.05).

Table 4.4. Distribution of bleeding status of infants by their maternal religion

Religion	**Infants who had bleeding** n=3039		**Infants who did not have bleeding** n=26770	
	No.	%	No.	%
Islam	2824	92.9	24553	91.7
Hindu	211	6.9	2159	8.1
Others	4	0.1	58	0.2
Pearsons Chi^2(2)= 5.7025				*p-value <0.05*

4.5 Parental Education

Comparison of maternal education of infants who had bleeding and who did not have showed that nearly half of the mothers in both groups of infants were illiterate (Table 4.5). The median year of schooling for mothers of infants who had bleeding was 1 ± 3.4 year compared to 2 ± 3.9 years for mothers of infants who did not have bleeding (p=<0.05). Over 50% of the fathers of infants who had bleeding and who did not have were illiterate (Table 4.5). Percentage distributions were very similar for different levels of parental education in both types of infants.

Table 4.5: Distribution of bleeding status of infants by their parental education

Maternal Education	**Infants who had bleeding** n=3039		**Infants who did have bleeding** n=26770	
	No.	%	No.	%
Illiterate	1497	49.3	12824	47.9
Primary	598	19.7	4919	18.4
Secondary	346	27.8	7928	29.6
Higher	96	3.2	1089	4.1
Don't know	2	0.1	10	0.04
Pearsons Chi ^{2}(4)= 12.696				*p-value <0.01*
Mean (in years)		3.36		3.59
Median (in years)		1.0		2.0
SD±		3.38		3.99
Ranksum test Z=2.591				*p-value <0.05*

Fathers' Education	**Infants who had bleeding** n=3039		**Infants who did not have bleeding** n=26770	
	No.	%	No.	%
Illiterate	1653	54.4	13979	52.2
Primary	436	14.4	3880	14.5
Secondary	565	18.6	5323	19.9
Higher	246	8.1	2338	8.7
Don't know	139	4.6	1250	4.7
Pearsons Chi^2(4) 6.1474				*p-value : 0.188*
Mean		3.3		3.6
Median		0		0
SD±		4.39		4.49
Ranksum test Z=2.487				*p-value: <0.001*

4.6 Parental Occupation

When bleeding status of infants were analyzed with their parental occupations, over 80% of the mothers of both types of infants were not engaged in any type of earning jobs. Percentage distributions of bleeding status of infants were similar for the different categories of maternal occupations. Percentage distributions of bleeding status of infants were also similar for the different categories of fathers' occupations (Table 4.6).

Table 4.6: Distribution of bleeding status of infants by their parental occupation

Maternal Occupation	**Infants who had bleeding** n=3039		**Infants who did not have bleeding** n=26770	
	No.	%	No.	%
No earning job	2539	83.6	22666	84.7
Farmer	3	0.1	22	0.1
Laborer	26	0.9	180	0.7
Business	414	13.6	3409	12.7
Service	52	1.7	446	1.7
Others	5	0.2	46	0.2
Don't Know	0	0	1	0
Pearsons Chi^2 (6) 3.6553				*p-value: 0.723*
Fathers' Occupation	**Infants who had bleeding** n=3039		**Infants who did not have bleeding** n=26770	
	No.	%	No.	%
Farmer	828	27.3	7241	27.1
Laborer	795	26.2	7329	27.4
Business	1100	36.2	9387	35.1
Service	230	7.6	2179	8.1
Others	86	2.8	624	2.3
Don't Know	0	0	9	0.03
Pearsons Chi^2 (5) 7.492				*p-value: 0.187*

4.7 Maternal 3rd Trimester MUAC

In analyzing bleeding status of infants with maternal mid upper arm circumference (MUAC) measured at 3rd trimester of pregnancy, over 45% of mothers in both categories of infants had a MUAC below 22.5 cm (Table 4.7). The mean MUAC of mothers of infants who had bleeding was 22.96 ± 1.9 cm compared to 22.84 ± 1.9 cm for mothers of infants who did not have bleeding (p= <0.05).

Table 4.7: Distribution of bleeding status of infants* by their maternal 3rd trimester MUAC

Maternal 3rd Trimester MUAC (in cm)	**Infants who had bleeding** n=1096		**Infants who did not have bleeding** n=11268	
	No.	%	No.	%
15.1-20	50	4.6	601	5.3
20.1-22.5	445	40.6	4738	42.1
22.6-25	466	42.5	4621	41.0
25.1-37	134	12.2	1281	11.4
Don't Know /Refused	1	0.1	27	0.2
Pearsons Chi²(4) 3.7934				*p-value: 0.435*
Mean (in cm)	22.96		22.84	
Median (in cm)	22.8		22.7	
SD±	1.91		1.91	
T-test	*T=-2.0028*			*p-value: <0.05*

** The numbers changed as the 3rd trimester maternal interview was started later*

4.8 Place, Attendants and Types of Delivery

Detailed data were collected on the index deliveries at the 3-month postpartum visits of mothers. When the bleeding status of infants was examined based on the place of delivery, around 95% of the mothers in both groups of infants were found to be delivered at home. The percentage distributions of infants who had bleeding and who did not have bleeding were very similar for the rest of the categories for delivery place of mothers (Table 4.9). The mothers were asked about the birth attendants of their index deliveries (Table 4.9). Nearly 90% of mothers in both categories of infants were found to be delivered by untrained birth attendants that included self, friends/relatives, traditional birth attendants and village doctors. The percentage distributions of infants who had bleeding and who did not have were similar for different types of birth attendants except for friends/relatives (75.5% vs. 73.4%) and TBA (16.6% vs. 19.0%) for infants who had bleeding and who did not have, respectively.

Mothers were asked at the 3 months post partum visit whether they had any obstructed labor during the index delivery. Higher percentages of mothers of infants who had bleeding reported to have obstructed labor than mothers of infants who did not have bleeding (17.3 vs. 15.3%, $p=<0.005$).

Table 4.8: Distribution of bleeding status of infants* by place, attendants and types of delivery

Place of Delivery	Infants who had bleeding n=3009		Infants who did not have bleeding n=26433	
	No	%	No	%
Home (parental, friends', neighbors')	2872	95.5	25052	94.8
FWC/THC/MCWC	52	1.7	513	1.9
District hospital/ medical college	49	1.6	481	1.8
Private clinic	19	0.6	257	0.9
On they way to hospital	5	0.2	46	0.2
Others	12	0.4	80	0.3
Don't Know	0	0	4	0.02
Pearsons Chi^2 (6)= 5.9255				*p-value: 0.432*

Birth Attendants	Infants who had bleeding n=3009		Infants who did not have bleeding n=26433	
	No.	%	No.	%
None	73	2.4	479	1.8
Friends/relatives	2273	75.5	19392	73.4
TBA	498	16.6	5020	19.0
Village doctors	31	1.0	232	0.9
FWA/FWV/SACMO/MA	93	3.1	881	3.3
MBBS doctors	40	1.3	409	1.6
Others	0	0	4	0.02
Don't Know	1	0.03	16	0.1
Pearsons Chi^2(7) =18.5885				*p-value: <0.01*

Type of Delivery	Infants who had bleeding n=3009		Infants who did not have bleeding n=26431	
	No	%	No	%
Not obstructed labor	2466	81.9	22091	83.6
Obstructed labor	519	17.3	4049	15.3
Don't Know	24	0.8	291	1.1
Pearsons Chi^2(2)= 9.6590				*p-value: < 0.005*

* *The numbers changed for maternal 3-month post partum visit completion*

4.9 Summary Findings of Chapter 4

In this chapter the bleeding status of infants were analyzed vis-à-vis parental characteristics e.g. maternal age, maternal parity, religion, education, occupation, maternal MUAC and maternal DGLV consumption during 3rd trimester of pregnancy and 3-month post partum period. The bleeding status of infants was also analyzed for maternal delivery characteristics e.g. place of delivery, birth attendants and type of deliveries. In the study cohort, there were 29,844 live born infants at the outset. Among 26,705 surviving infants, 2395 (8.9%) had any bleeding symptom and among 3139 deceased infants, 650 (20.7%) had any bleeding symptom. Among the cohort of all live born infants 3045 (10.2%) infants had any bleeding symptom.

Mothers of infants who had bleeding were slightly older than mothers of infants who did not have bleeding (p=<0.001) with mean age 22.4 ± 6.1years and 21.9 ± 5.7 years, respectively. Similarly, mothers of infants who had bleeding were more parous than mothers of infants who did not have bleeding. Percentages of infants who had bleeding were less among Hindu mothers compared to that of infants who did not have bleeding. More than half of the parents were illiterate and had similar types of occupation for both types of infants.

Mothers of infants who had bleeding had a little higher MUAC (22.84 ± 1.91 cm; p= <0.05) than mothers (22.96 ± 1.91 cm) of infants who did not have bleeding. About 95% of mothers of both types of infants were delivered at home and most of them were attended by their untrained relatives. Higher percentages of mothers of infants who had bleeding reported to have obstructed labor than mothers of infants who did not have bleeding (17.3 vs. 15.3%, p=<0.005).

Chapter 5: Characteristics of Infants

This chapter deals with the analyses of the bleeding status of infants with some of the infants' characteristics e.g. gender, number of siblings, maturity at birth, birth weights, and time of initiation and type of crying at birth. Time and type of crying was considered as a proxy of birth asphyxia for this analysis.

5.1 Gender and Number of Siblings

On analysis of the bleeding status of infants by their gender, it was found that bleeding was reported in a significantly higher ($p =<0.005$) percentage among male infants compared to the female infants (53.3% vs. 46.7%).

Table 5.1: Distribution of bleeding status by gender and number of siblings of infants

Gender	**Infants who had bleeding** n=3045		**Infants who did not have bleeding** n=26799	
	No.	%	No.	%
Male	1624	53.3	13598	50.7
Female	1421	46.7	13201	49.3
Pearsons $Chi^2(1)$ =7.3547				*p-value: <0.005*
Number of Siblings	**Infants who had bleeding** n=3045		**Infants who did not have bleeding** n=26799	
	No.	%	No.	%
Singleton	2945	96.7	26298	98.1
Twins	96	3.2	463	1.7
Triplets/quadruplets	4	0.1	38	0.1
Pearsons $Chi^2(2)$= 30.2240				*p-value:< 0.0001*

Similarly, when the bleeding status of infants were analyzed by the number of siblings in the index delivery (Table 5.1), the percentage of twins were higher among infants who had bleeding compared to the infants who did not have bleeding (3.2% vs. 1.7%) and the difference was statistically significant (p = < 0.0001).

5.2 Maturity at Birth

The maturity at birth was determined in weeks by the best guess gestational age calculation based on the pregnancy tests utilizing maternal urine, maternal reporting of last week of menstrual period and the date of delivery.

Table 5.2: Distribution of bleeding status of infants by their maturity at birth

Gestational Age at Birth (in weeks)	**Infants who had bleeding**		**Infants who did not have bleeding**	
	n=3020		n=26637	
	No.	%	No.	%
28-32 weeks	298	9.9	1741	6.5
33-36 weeks	647	21.4	5309	19.9
37-41 weeks	1878	62.2	17695	66.4
42+ weeks	197	6.5	1892	7.1
Pearsons Chi^2 (3)= 55.498				*p-value: <0.0001*
Mean (in weeks)	37.4		37.8	
Median (in weeks)	38.0		38.0	
SD±	3.33		3.04	
t-test	*t=7.039*		*p-value: <0.0001*	

The percentage distribution of very premature (28 to 32 weeks of gestation) babies was 9.9% in infants who had bleeding compared to 6.5% in infants who did not have bleeding.

Similarly, the distribution of premature babies with a gestational age ranging between 33 to 36 weeks was 21.4% in infants who had bleeding compared to 19.9% in infants who did not have bleeding (Table 5.2). On the other hand, the percentage of mature babies (ranging 37 to 41 weeks of gestation) was 62.2% in infants who had bleeding compared to 66.4% in infants who did not have bleeding.

The mean gestational age at birth was 37.4 ± 3.3 weeks for infants who had bleeding compared to 37.8 ± 3.0 weeks for infants who did not have bleeding, the difference being statistically significant ($p=<0.0001$), indicating that infants who had bleeding had a comparatively less gestational age than infants who did not have bleeding at birth.

5.3 Birth Weights

As the infant trial started later (mid way) than the maternal trial, birth weights for all infants were not available. Birth weights of ~14000 infants were measured and only those babies who could be measured within 48 hours of birth were included in this analysis (Table 5.3).

Table 5.3: Distribution of bleeding status of infants by their birth weights (measured within 48 hours of birth)

Birth Weights (in kg)	**Infants who had bleeding** n=1041		**Infants who did not have bleeding** n=10202	
	No.	%	No.	%
0.68-1.49	48	4.6	219	2.2
1.5-1.99	116	11.1	1244	12.2
2-2.49	401	38.5	4183	41.0
2.5-2.99	376	36.1	3621	35.5
3-3.49	80	7.7	795	7.8
3.5-3.98	9	0.9	75	0.7
Don't Know /Refused	11	1.1	65	0.6
Pearsons Chi^2(6) =29.2332				*p-value: <0.001*
Mean (in kg)	2.42		2.43	
Median (in kg)	2.45		2.43	
SD±	0.471		0.428	
t-test	*t=0.7372*			*p-value: 0.461*

The percentage distribution of extremely low birth weights (below 1.50 kg) was 4.6% in the infants who had bleeding compared to 2.2% in the infants who did not have bleeding. The percentage distribution of birth weights ranging 2-2.49 kg was 38.5% in infants who had bleeding compared to 41.0% in the infants who did not have bleeding.

The mean birth weight for infants who had bleeding category was 2.42 ± 0.47 kg compared to 2.43 ± 0.43 kg for infants who did not have bleeding category, which were very similar (p = 0.460).

5.4 Initiation Time and Type of Crying of Surviving Infants

During the 3 month follow up visits, the mothers were asked of their surviving infants about the time and types of their crying after births. The time and type of crying (as proxy for birth asphyxia status) were analyzed for the surviving infants to see whether birth asphyxia had any effect on their bleeding status (Table 5.4).

Table 5.4 Distribution of bleeding status by time of initiation and type of crying of surviving infants

Time of Crying After Birth	**Infants who had bleeding** n=2385		**Infants who did not have bleeding** n=24074	
	No.	%	No.	%
Within one minute	1831	76.8	18779	78.0
After one minute	509	21.3	4821	20.0
Don't Know	45	1.9	474	2.0
Pearsons Chi^2(2) = 2.3642				*p-value: 0.307*
Types of Crying	**Infants who had bleeding** n=2385		**Infants who did not have bleeding** n=24074	
	No.	%	No.	%
Did not cry/weak cry	631	26.5	6438	26.7
Cried normally	1719	72.1	17146	71.2
Don't Know	35	1.5	490	2.0
Pearsons Chi^2(2)= 3.8148				*p-value: 0.148*

It was found that similar proportion of surviving infants who had and who did not have bleeding started crying within one minute of birth (76.8% vs. 78%). Similar percentages of both types of surviving infants did not cry/cried weakly after birth (26.5% vs. 26.7%).

5.5 Initiation Time and Type of Crying of Deceased Infants

The time and type of crying after birth in the deceased infants group were also analyzed as a proxy of birth asphyxia. This was done to see whether there was any effect on their bleeding status (Table 5.5). The mothers were asked during the verbal autopsies of their deceased infants about the time and types of their crying after births.

Table 5.5: Distribution of bleeding status by time of initiation and type crying of deceased infants

Time of Crying After Births	**Infants who had bleeding** n=650		**Infants who did not have bleeding** n=2439	
	No.	%	No.	%
Within one minute	434	66.8	1565	64.2
After one minute	192	29.5	738	30.3
Don't Know	24	3.7	136	5.6
Pearsons Chi^2(2) = 4.1419				*p-value: 0.126*
Type of Crying	**Infants who had bleeding** n=650		**Infants who did not have bleeding** n=2439	
	No	%	No	%
Did not cry/weak cry	319	49.1	1264	51.8
Cried normally	309	47.5	1088	44.6
Don't know	22	3.4	87	3.6
Pearsons Chi^2(2)= 1.7787				*p-value: 0.411*

When the bleeding status of deceased infants were analyzed by how long after birth they started crying, a slightly higher proportion of deceased infants who had bleeding (66.8%) started crying within one minute of birth as compared to the infants who did not have bleeding (64.2%). However this difference was not statistically significant (p =0.126). In the bleeding status of deceased infants by type of crying, similar proportions of both infants who had bleeding and who did not have did not cry/cried weakly after birth (49.1% vs. 51.8%).

5.6 Summary Findings of Chapter 5

In this chapter the bleeding status of infants were analyzed with their characteristics e.g. gender, number of siblings, maturity at birth, birth weights, and time of initiation and type of crying at birth. Time and type of crying was considered as proxy indicators of birth asphyxia in this analysis.

Male infants had a significantly higher percentage ($p = <0.005$) of bleeding than female infants (53.3% vs. 46.7%). Twin infants were in significantly higher percentages (3.2% vs. 1.7%) among the infants who had bleeding than in infants who did not have bleeding ($p = <0.0001$; Table 5.1).

Premature infants (<37 weeks of gestation) were in significantly higher percentages ($p = <0.0001$) among the infants who had bleeding than infants who did not have bleeding (31.3% vs. 26.4%; Table 5.2). Higher percentages of extremely low birth weight (<1.5kg) infants were in higher percentages among infants who had bleeding than infants who did not have bleeding (4.6% vs. 2.2%; Table 5.3). When the time of initiation and types of crying as proxies for birth asphyxia were analyzed, no differences in bleeding status for both surviving (Table 5.4) and deceased infants (Table 5.5) were found.

Chapter 6: Morbidities of Infants

This chapter deals with the analysis of the bleeding status of infants with the morbidities they suffered from. Mothers were asked whether their surviving infants suffered from cough/cold, high fever, diarrhoea and dysentery in the last 3 months during the 6-month follow up visits. On the other hand, mothers were asked during the verbal autopsies; whether their deceased infants suffered from cough/cold, cough with high fever, breathing difficulties, diarrhoea and dysentery in the 7 days of deaths.

6.1 Cough/Cold and High Fever of Surviving Infants

Mothers were asked whether their surviving infants suffered from cough/cold in the last 3 months during the 6-month follow up interviews.

Table 6.1: Distribution of bleeding status of surviving infants by cough/cold and high fever in last 3 months

Cough/Cold in Last 3 Months	**Infants who had bleeding** n=2395		**Infants who did not have bleeding** n=24028	
	No.	%	No.	%
No	212	8.9	3357	13.9
Yes	2182	91.1	20670	86.0
Don't Know	1	0.1	1	0
Pearsons $Chi^2(2)$= 52.8285				*p-value: <0.001*
High Fever in Last 3 Months	**Infants who had bleeding** n=2395		**Infants who did not have bleeding** n=24026	
	No.	%	No.	%
No	736	30.7	9880	41.1
Yes	1658	69.2	14141	58.9
Don't Know	1	0.1	5	0
Pearsons $Chi^2(2)$ = 98.1206				*p-value: ≤0.001*

When the bleeding status of surviving infants were analyzed with whether they suffered from cough/cold in the last 3 months, a significantly higher proportion (p=<0.001) of infants who had bleeding (91.1%) suffered from cough/cold than infants who did not have bleeding (86.0%; Table 6.1). Similarly, when this was analyzed with whether surviving infants suffered from high fever in last 3 months, a significantly higher proportion of infants who had bleeding suffered from high fever than those infants who did not have bleeding (69.2% vs. 58.9%, p=<0.001).

6.2 Diarrhoea and Dysentery of Surviving Infants

When the bleeding status of surviving infants was analyzed with whether the infants suffered from diarrhoea in the last 3 months, a significantly higher proportion of surviving infants who had bleeding suffered from diarrhoea than infants who did not have bleeding (25% vs. 15.3.%; p=<0.001; Table 6.2).

Table 6.2: Distribution of bleeding status of surviving infants by diarrhoea and dysentery in last 3 months

Diarrhoea in Last 3 Months	**Infants who had bleeding** n=2395		**Infants who did not have bleeding** n=24024	
	No.	%	No.	%
No	1796	74.9	20354	84.7
Yes	599	25.0	3667	15.3
Don't Know	0	0	3	0
Pearsons Chi²(2) = 153.0861			*p-value: <0.001*	
Dysentery in 3 Last Months	**Infants who had bleeding** n=2395		**Infants who did not have bleeding** n=24026	
	No.	%	No.	%
No	1578	65.9	22849	95.1
Yes	817	34.1	1175	4.9
Don't Know	0	0	2	0
Pearsons Chi²(2) = 2700			*p-value:< 0.001*	

When it was looked into whether surviving infants suffered from dysentery in the past 3 months, a significantly higher proportion of infants who had bleeding was seen to be suffering from dysentery than the infants who did not have bleeding (34.1% vs. 4.9%; p=<0.001).

6.3 Fresh Intestinal Bleeding during Dysentery among Surviving Infants

The distribution of fresh intestinal bleeding (red blood in stool) status of surviving infants were investigated to see whether they suffered from dysentery in the last 3 months (Table 6.3). It was found that a higher proportion of infants (86.6%) who had fresh intestinal bleeding compared to those who did not have fresh intestinal bleeding (5.1%) suffered from dysentery in last 3 months. This difference was statistically significant (p=<0.001).

Table 6.3: Distribution of fresh bleeding status of surviving infants by dysentery in last 3 months

Dysentery in Last 3 Months	**Infants who had fresh bleeding** n=791		**Infants who did not have fresh bleeding** n=25630	
	No.	%	No.	%
No	106	13.4	24321	94.9
Yes	685	86.6	1307	5.1
Don't Know	0	0	2	0
Pearsons Chi²(2) = 7300			*p-value: <0.001*	

6.4 Cough/Cold with High Fever and Breathing Difficulties of Deceased Infants

During the verbal autopsies, mothers were inquired on whether their deceased infants had cough/cold within 7 days before their deaths. Similar proportion of infants who had bleeding (54.6%) and infants who did not have bleeding (53.2%) suffered from cough/cold within 7 days before their deaths (Table 6.4).

Table 6.4: Distribution of bleeding status of deceased infants by cough, cough with high fever and breathing difficulties in 7 days prior to death

Cough/Cold in 7 days prior to death	**Infants who had bleeding** n=370		**Infants who did not have bleeding** n=1274	
	No.	%	No.	%
No	166	44.9	580	45.5
Yes	202	54.6	678	53.2
Don't Know	2	0.5	16	1.3
Pearsons Chi²(2) = 1.4692				*p-value: 0.480*
Cough with High Fever in 7 days prior to death	**Infants who had bleeding** n=201		**Infants who did not have bleeding** n=678	
	No.	%	No.	%
No	81	40.3	231	34.1
Yes	118	58.7	443	65.3
Don't Know	2	1.0	4	0.6
Pearsons Chi²(2)= 3.1354				*p-value: 0.209*
Breathing Difficulties in 7 days prior to death	**Infants who had bleeding** n=370		**Infants who did not have bleeding** n=1274	
	No.	%	No.	%
No	150	40.5	568	44.6
Yes	217	58.7	691	54.2
Don't Know	3	0.8	15	1.2
Pearsons Chi²(2) = 2.4349				*p-value: 0.296*

When their bleeding status was analyzed by cough accompanied with high fever within 7 days before the death of deceased infants, higher proportion of infants who did not have bleeding (65.3%) were seen to suffer from cough accompanied by high fever than infants who had bleeding (58.7%), but the difference was not statistically significant (p=0.209). Similarly mothers were asked whether their deceased infants had breathing difficulties within the 7 days of deaths during the verbal autopsies. Higher proportions of infants who had bleeding (58.7%) suffered from breathing difficulties than their counterparts (54.2%) in the 7 days prior to their deaths (the difference was not statistically significant; p= 0.296).

6.5 Diarrhoea and Dysentery of Deceased Infants

During the verbal autopsies, mothers were asked whether their deceased infants suffered from diarrhoea in the 7 days prior to their deaths.

Table 6.5: Distribution of bleeding status of deceased infants by diarrhoea and dysentery in 7 days prior to death

Diarrhoea in 7 days prior to death	**Infants who had bleeding**		**Infants who did not have bleeding**	
	n=394		n=1370	
	No.	%	No.	%
No	344	87.3	1169	85.3
Yes	50	12.7	185	13.5
Don't Know	0	0	16	1.2
Pearsons Chi^2(2) = 4.8934			*p-value: 0.087*	
Dysentery in 7 days prior to death	**Infants who had bleeding**		**Infants who did not have bleeding**	
	n=394		n=1370	
	No.	%	No.	%
No	361	91.6	1327	96.9
Yes	33	8.4	25	1.8
Don't Know	0	0	18	1.3
Pearsons Chi^2(2)= 45.5910			*p-value:< 0.001*	

When the bleeding status of deceased infants were analyzed with whether they had diarrhoea within 7 days of their deaths (Table 6.5), similar proportion of both infants who had bleeding and who did not were seen to be suffering from diarrhoea (12.7% vs. 13.5% respectively). Similarly, when analyzing the bleeding status of deceased infants with whether they suffered from dysentery 7 days prior to their deaths, higher proportion of infants who had bleeding (8.4%) suffered from dysentery than infants who did not have bleeding (1.8%), the difference was statistically significant (p=<0.001).

6.6 Fresh Intestinal Bleeding during Dysentery of Deceased Infants

When distributions of deceased infants' fresh intestinal bleeding (Table 6.6) were examined with dysentery within 7 days prior to their deaths, a higher proportion of infants were found to have had fresh intestinal bleeding (60%) compared to those who did not have fresh intestinal bleeding (1.6%) suffering from dysentery within 7 days prior to deaths and the difference was statistically significant (p=<0.001).

Table.6.6: Distribution of fresh intestinal bleeding status of deceased infants by dysentery in 7 days prior to death

Dysentery in 7 days prior to death	**Infants who had fresh bleeding** n=50		**Infants who did not have fresh bleeding** n=1714	
	No.	%	No.	%
No	20	40.0	1668	97.3
Yes	30	60.0	28	1.6
Don't Know	0	0	18	1.1
Pearsons Chi^2(2) = 520.5637			*p-value:< 0.001*	

6.7 Summary Findings of Chapter 6

This chapter showed analysis for the bleeding status of infants with their reported morbidities. When the bleeding status was analyzed with morbidities in the last 3 months of surviving infants, significantly higher proportion of infants who had bleeding suffered from cough/cold, high fever, diarrhoea and dysentery than infants who did not have bleeding (Table 6.1 and Table 6.2). About 87% of surviving infants had fresh intestinal bleeding while suffering from dysentery in the last 3 months (Table 6.3).

When the bleeding status with morbidities of deceased infants in the last 7 days prior to death were analyzed, no difference was detected in the bleeding status for morbidities like cough, cough with high fever, breathing difficulties and diarrhoea (Table 6.4 and Table 6.5). Significantly higher proportion of infants who had bleeding (8.4% vs. 1.8%) suffered from dysentery than infants who did not have bleeding ($p=<0.001$). About 60% of deceased infants who had fresh intestinal bleeding suffered from dysentery (Table 6.6).

Chapter 7: Incidence and Case Fatality Rates

In this chapter distributions of the bleeding symptoms and calculated incidence rates per 1000 infants have been examined. In addition to that case fatality rates with 95% confidence interval (CI) associated with bleeding symptoms also been presented. Estimates were reported for individual bleeding symptoms e.g. nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding, dark stool, bulging fontanel and combinations of bleeding symptoms such as nasal bleeding with either (a) bruising, or (b) bulging fontal, or nasal bleeding with either (c) bruising or umbilical bleeding. Estimates were also generated for being positive for any of the symptoms of bleeding. Symptoms were combined like this to evaluate the potential that they could confer different levels of risk for mortality of infants. Outcomes related to individual and combined symptoms were classified as early onset (<24 hours of age), classical (occurring between 2 and 7 days of age) or late in their onset (occurring from 8 days-to-6months of age) following the conventional classification system for vitamin K-deficiency associated bleeding disorders[3].

7.1 Age Interval-Specific Mortality Rates

Vital status data were available for 29,844 live born infants, among whom 1203 died within 24 hours of birth resulting in a mortality rate of 40.3 deaths per 1000 live births in the first day of life (Table 7.1).

Table 7.1: Interval mortality rates in 1000 live births

Age interval	No. Alive at start of interval	No. of deaths in interval	Interval mortality rate/1000 infants	Interval mortality rate/1000 live births	Cumulative infant mortality rate/1000 live births
Early (0-24 hrs)	29844	1203	40.3	40.3	40.3
Classical (2-7 d)	28641	738	25.8	24.7	65.0
Late (8 d to 6 mo)	27903	1198	42.9	40.1	105.2
Total (0 d to 6 mo)	29844	3139	105.2	105.2	105.2

This also led to a reduction in the size of the cohort of infants who died by six months of age to 1936 after the first 24 hours of birth, a number which also served as the denominator for incidence estimation during the classic (2 to 7 day of age) time period.

Another 738 infants died between the age of 2 and 7 days, resulting in a mortality rate of 25.8 deaths per 1000 among infants who had survived up to day 7 of age or, giving a mortahty rate of 24.7 per 1000 hve births. Thus, the early neonatal mortality rate (i.e. reflecting risk of death in the first 7 days of life) was 65.0 per 1000 live births. This mortality experience left the remaining 1198 infants who survived the first week of life but died between 8 days and 6 months of age. Their deaths resulted in a late interval-specific mortality rate of 42.9 deaths per 1000 infants or 40.1 deaths per 1000 live births.

The cumulative mortality rate of infants up to 6 months of age was 105.2 per 1000 live births, reflecting a substantially higher risk of death in the first six months of life than estimated nationally. The total number of infants who died in the first six months of life was 3,139, which represents the full analytic cohort of infants who were deceased by six months of age. Thus, the number of infants who survived up to 6 months of age was 26,705, which represented the full cohort of surviving infants in this analysis.

7.2 Bleeding Symptoms: Proportionate Reporting by Age

Bleeding symptoms by the age intervals were tabulated based on the symptoms that were reported by parents during the home interview by trained field staff at about six months of age for surviving infants, and typically within 1 to 2 months following the death of an infant during the course of a verbal autopsy interview, also carried out by trained female interviewers. The actual and proportionate distributions of the bleeding symptoms for each age interval (early, classic and late) are given in Table 7.2 for infants in the surviving and deceased cohorts.

Among 26,705 infants who survived up to 6 months of age, 2395 (9.0%) were reported to have had any bleeding symptoms at any time up to that age by their parents (Table 7.2), defined as a history of nasal bleeding, bruising, umbilical bleeding, bright red blood in stool (reflecting fresh intestinal bleeding), dark stool, bleeding during circumcision (data not shown), or a bulging fontanel (as a non-specific symptom of possible intracranial bleeding). In contrast, among the 3139 infants who died at 6 months of age, 650 (20.7%) were reported by parents to have had any symptoms of bleeding prior to death, reflecting a frequency that was 2.3 times greater than among surviving infants.

Thus, of all 29,844 infants in the study, including both survivors and infants who later died by age six months, parents reported symptoms of bleeding in 3045 or 10.2% of all study infants. To explore this distribution further, each bleeding symptom was classified by age of onset, as early (<24hours), classical (2 days to 7 days) and late (8 days to 6 months) onset. Higher proportions of infants who died in the first six months had early and classic onset of bleeding symptoms than surviving infants (38.8% vs. 7.4% and 33.9% vs. 21.9%, respectively), reflecting both the possibility that early occurrence of bleeding was more likely to be fatal than later bleeding (see Section 7.5), but also the fact that fewer infants in the deceased cohort survived to the older ages. Among surviving infants, 66.7% reported as initial or only episode of bleeding beyond the first week of life.

Ninety five surviving infants (4%) and 205 deceased infants (31.5%) were reported to have had nasal bleeding (Table 7.2). Higher proportions of infants who eventually died had nasal bleeding during all three age intervals (12.5% vs. 0.1%, 12.6% vs. 0.4%, and 6.2% vs. 3.4% respectively) than surviving infants. The thin nasal mucosum over the Kiesselbach plexus, an area in the anterior septum where vessels from the internal carotid, external carotid and terminal branches of the internal maxillary artery converge, could make it more susceptible to bleeding in infancy[13] but also may be among the most accessible vascular areas to reflect systemic vessel weakness and vulnerability to cranial hemorrhage.

One hundred and twenty seven surviving infants (5.3%) versus 96 infants (14.8%) who later died were reported to have had body bruising, with higher proportions in the latter group reporting early (9.5% vs. 0.7%) and classical (2.5% vs. 0.3%) onset than their surviving counterparts (Table 7.2). Umbilical bleeding was the most common type of reported bleeding in both cohorts with 977 surviving infants (40.8%) and 227 infants in the deceased cohort (34.9%) being reported by parents to have had the condition (Table 7.2). A higher proportion of infants who later died were reported to have had umbilical bleeding in the first day of life compared to surviving infants (15.7% vs. 5.1%), suggesting that (excessive) umbilical bleeding in the first day of life could be, or reflect, a potentially fatal condition.

On the other hand, comparable proportions in both groups had umbilical bleeding in the rest of the 1st week of life, leaving a higher proportion of surviving than deceased infants reported as onset of umbilical bleeding beyond the first week of life (15.5% vs. 4.8%). Fresh intestinal bleeding, recalled by parents as bright red blood in an infant's stools, was reported by parents of 791 surviving infants (33.0%), nearly 90% of which appeared to occur after the first week of life. Its rare occurrence in the first 7 days of life and relative predominance thereafter in both cohorts of infants suggests this symptom as being indicative of dysentery rather than reflecting a potentially fatal, innate impairment at or shortly after birth (Table 7.2).

Two hundred seventeen surviving infants (9.1%) and 60 infants who later died (9.2%) reported to have dark stools, suggestive of upper gastrointestinal bleeding (Table 7.2).

Table 7.2: Proportionate distributions of bleeding symptoms by type and age of onset among infants who survived or died by six months of age

Symptoms	Surviving Infants with Any Reported Bleeding (n= 2395)		Infants with Any Bleeding Reported Before Death (n=650)		Total No of Infants in Study Cohort with Any Bleeding (n=3045)	
	n	%	n	%	n	%
Any Bleeding	2395	100	650	100	3045	100
Early (<24 hours)	177	7.4	252	38.8	429	14.1
Classical (2d-7d)	524	21.9	220	33.9	744	24.4
Late (8d-6months)	1597	66.7	160	24.6	1757	57.7
Don't Know	97	4.1	18	2.8	115	3.8
Nasal Bleeding	95	4.0	205	31.5	300	9.9
Early (<24 hours)	2	0.1	81	12.5	83	2.7
Classical (2d-7d)	9	0.4	82	12.6	91	2.9
Late (8d-6months)	81	3.4	40	6.2	121	3.9
Don't Know	3	0.1	2	0.4	5	0.2
Bruising	127	5.3	96	14.8	223	7.3
Early (<24 hours)	16	0.7	62	9.5	78	2.6
Classical (2d-7d)	8	0.3	16	2.5	24	0.8
Late (8d-6months)	99	4.1	15	2.3	114	3.7
Don't Know	4	0.2	3	0.5	7	0.2
Umbilical Bleeding	977	40.8	227	34.9	1204	39.5
Early (<24 hours)	122	5.1	102	15.7	224	7.4
Classical (2d-7d)	468	19.5	94	14.5	562	18.5
Late (8d-6months)	372	15.5	31	4.8	403	13.2
Don't Know	15	0.6	0	0	15	0.5
Red Blood in Stool	791	33.0	50	7.7	841	27.6
Early (<24 hours)	9	0.4	2	0.3	11	0.4
Classical (2d-7d)	35	1.5	10	1.5	45	1.5
Late (8d-6months)	705	29.4	36	5.5	741	24.3
Don't Know	42	1.8	2	0.3	44	1.4
Dark Stool	217	9.1	60	9.2	277	9.1
Early (<24 hours)	0	0	0	0	0	0
Classical (2d-7d)	30	1.3	28	4.3	58	1.9
Late (8d-6months)	171	7.1	28	4.3	199	6.5
Don't Know	16	0.7	4	0.6	20	0.7
Bulging Fontanel	348	14.5	111	17.1	459	15.1
Early (<24 hours)	41	1.7	40	6.2	81	2.7
Classical (2d-7d)	24	1.0	26	4.0	50	1.6
Late (8d-6months)	262	10.9	37	5.7	299	9.8
Don't Know	21	0.9	8	1.2	29	0.9

Continuation of Table 7.2:

Combination of Symptoms	Surviving Infants with Any Reported Bleeding (n= 2395)		Infants with Any Bleeding Reported Before Death (n=650)		Total No of Infants in Study Cohort with Any Bleeding (n=3045)	
	N	%	n		n	%
Any Nasal Bleeding or Bruising	222	9.3	289	44.5	511	16.8
Early (<24 hours)	18	0.8	136	20.9	154	5.1
Classical (2d-7d)	17	0.7	96	14.8	113	3.7
Late (8d-6months)	180	7.5	53	8.2	233	7.7
Don't Know	7	0.3	4	0.6	11	0.4
Any Nasal Bleeding or Bulging Fontanel	438	18.3	300	46.2	738	24.2
Early (<24 hours)	43	1.8	113	17.4	156	5.1
Classical (2d-7d)	33	1.4	104	16.0	137	4.5
Late (8d-6months)	339	14.2	73	11.2	412	13.5
Don't Know	23	0.9	10	1.5	33	1.1
Any Nasal Bleeding or Bruising or Umbilical Bleeding	1191	49.7	484	74.5	1675	55.0
Early (<24 hours)	137	5.7	223	34.3	360	11.8
Classical (2d-7d)	478	19.9	171	26.3	649	21.3
Late (8d-6months)	546	22.8	78	12.0	624	20.5
Don't Know	30	1.3	12	1.8	42	1.4

Reporting of dark stool in the first two days after birth was avoided to remove the confusion with meconium at birth being reported as dark stools, thereby presumably improving the specificity of parents' responses. Slightly higher proportion of deceased infants had dark stools than surviving infants for classical onset (4.3 % vs. 1.3%) while a higher proportion of parents of surviving infants reported dark stools (7.1% vs. 4.3%).

Comparable proportions of infants in both cohorts were reported to have had a bulging fontanel, 348 (14.5%) and 111 (17.1%) in the surviving and deceased cohorts, respectively, with the greater proportion occurring earlier in infants who died. Bulging fontanel during infancy could be a manifestation of intracranial bleeding[12], although it is more often understood to represent changes in intracranial blood flow volume and, if severe pressure[72]. It is possible that infants who died may have been more likely to suffer from intracranial bleeding episodes. Two hundred twenty two surviving infants (9.3%) and 289 deceased infants (44.5%) were reported to have had any nasal bleeding or bruising (Table 7.2). Higher proportions of infants who eventually died had this combination of bleeding during early and classic stages (i.e. within 7 days of life) (20.9% vs. 0.8% and 14.8% vs. 0.7%, respectively). During late stage the proportions were more similar (8.2% vs. 7.5% respectively) for deceased and surviving infants.

Higher proportion of deceased infants had combination of any nasal bleeding or bulging fontanel than surviving infants (46.2% vs. 18.3%). Proportions were higher for early and classic onset for deceased infants (17.4% vs. 1.8% and 16% vs. 1.4%, respectively) than surviving infants. Over all deceased infants had higher proportion of any nasal bleeding or bruising or umbilical bleeding (74.5%) than surviving infants (49.7%). Higher proportions of infants who died in the first six months had early and classic onset of this combination of bleeding symptoms than surviving infants (34.3% vs. 5.7% and 26.3% vs. 19.9%, respectively), reflecting both the possibility that early occurrence of this combination of bleeding could be more fatal than later bleeding.

On the other hand, a higher proportion was found for surviving infants (22.8%) than deceased infants (12.0%) for late onset of this combination of bleeding.

7.3 Incidence Rates of Bleeding Symptoms

Incidence rates were calculated on the basis of reported bleeding events (numerator) among infants who were alive at the outset of a specified age interval. Thus, among the surviving infants group, the denominator for the total and age-specific incidence rates was 26,705 as this number of infants survived up to six months of age.

However, the denominator for the cohort of infants who died by six months of age has been recalculated to reflect the number alive at birth, after the first day of life and after the seventh day of life, as they had to have been alive within the interval to be at risk of having a bleeding episode at that age. Thus, the denominators for infants in the deceased cohort were 3139, 1936 and 1198 for rates calculated for this cohort during the early (<24 hours), classic (2 to 7 days of age) and late (8 days to 6 months of age) periods, respectively.

Incidence rates were calculated for nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding, dark stool, bulging fontanel as well as for combinations of selected symptoms of bleeding; i.e. any nasal bleeding or bruising, any nasal bleeding or bulging fontanel, any nasal bleeding or either bruising or umbilical bleeding, and any of the bleeding symptoms based on the defined age intervals of onset. Total incidence rates for each symptom or combination of symptoms included a small fraction of infants for whom age at reported bleeding was not known. By necessity, they are excluded from the age-interval-specific incidence rates for the figures.

7.3.1 Incidence Rates of any Bleeding Symptoms

The overall incidence rate of any bleeding symptom was 102.0 per 1000 infants in the study cohort of surviving and deceased infants. The incidence of any bleeding was 89.7 per 1000 infants among surviving infants and 207 per 1000 infants in deceased infants (Table 7.3.1A) The relative risk was 2.3 (95% CI 2.1-2.5), reflecting 2.3 times greater risk of any bleeding in the cohort of infants who died by six months of age (Table 7.3.1B) compared to the surviving infants.

Table 7.3.1 A: Incidence rates of any bleeding per 1000 infants at outset of specified age intervals

Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased infants		Incidence of Bleeding in all Infants in Study Cohort	
	n	Incidence	n	Incidence	n	Incidence
Any Bleeding						
Early (<24 hours)	177	6.6	252	80.3	429	14.4
Classical (2d-7d)	524	19.6	220	113.6	744	26.0
Late (8d-6months)	1597	59.8	160	133.6	1757	63.0
Don't Know	97	3.6	18	5.7	115	3.6
Total	2395	89.7	650	207.0	3045	102.0

Table 7.3.1B: Relative risk of any bleeding symptoms at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	12.1	9.9-14.8
Classical (2d-7d)	5.8	4.9-6.8
Late (8d-6months)	2.2	1.9-2.7
Total	2.3	2.1-2.5

The deceased infants were 12.1 (95% CI 9.9-14.8), 5.8 (95% CI 4.9-6.8) and 2.2 (95% CI 1.9-2.7) times more likely to have had any bleeding during the early, classic and late periods, respectively, than the surviving cohort.

These indicate that any bleeding in the first day of life was associated with the highest risk of death in early infancy, but also that there was a dose-response gradient, with the risk of death seeming to decrease with reported older age at which any symptom of bleeding occurred.

7.3.2 Incidence Rates of Nasal Bleeding

The overall incidence rate of nasal bleeding was 10.1 per 1000 infants in the total cohort of surviving and deceased infants (Table 7.3. 2A). Among the bleeding symptoms investigated, a nosebleed appeared to be most strongly associated with the cohort of infants who died versus those who survived.

Table 7.3.2A: Incidence rates of nasal bleeding per 1000 infants at outset of specified age intervals

Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased Infants		Incidence of Bleeding in all Infants in Study Cohort	
Nasal Bleeding	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	2	0.07	81	25.8	83	2.8
Classical (2d-7d)	9	0.34	82	42.4	91	3.2
Late (8d-6months)	81	3.0	40	33.4	121	4.3
Don't Know	3	0.1	2	0.6	5	0.2
Total	95	3.6	205	65.3	300	10.1

Table 7.3.2B: Relative risk of nasal bleeding at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence interval
Early (<24 hours)	344.6	92.3-2893.4
Classical (2d-7d)	125.8	62.9-284.8
Late (8d-6months)	11.0	7.3-16.3
Total	18.4	14.3-23.7

Overall, at a relative risk of 18.4 (95% CI 14.3-23.7), nasal bleeding accounted for 31.5% of all symptomatic bleeding in the cohort of infants who died, whereas any nosebleed was exceedingly uncommon (3.9 per 1000 infants) among surviving infants.

Nasal bleeding occurring in the first day of life occurred virtually only in infants who died, with the relative risks being 344.6 (95% CI 92.3-2893.4), 125.8 (95%CI 62.9-284.8) and 11.1 (95% CI 7.3-16.3) during the early, classic and late periods, respectively compared to the survivors (Table 7.3. 2B).

7.3.3 Incidence Rates of Bruising

The overall incidence rate of bruising in the total cohort of surviving and deceased infants was 7.5 per 1000 infants. The incidence rates of bruising were 2.6, 0.8 and 4.1 in the total cohort at early, classic and late intervals respectively (Table 7.3.3A).

The relative risks of bruising were 32.9 (95% CI 18.8-61.3), 27.6 (95% CI 11.1-74.5) and 3.4 (95% CI 1.8-5.9) for early, classic and late intervals, reflecting deceased infants were more likely to have had bruising than the surviving infants at all three intervals of onset of bleeding (Table 7.3.3 B).

Table 7.3.3 A: Incidence rates of bruising per 1000 infants at outset of specified age intervals

Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased Infants		Incidence of Bleeding in all Infants in Study Cohort	
Bruising	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	16	0.6	62	19.8	78	2.6
Classical (2d-7d)	8	0.3	16	8.3	24	0.8
Late (8d-6months)	99	3.7	15	12.5	114	4.1
Don't Know	4	0.2	3	1.0	7	0.2
Total	127	4.8	96	30.6	223	7.5

Table 7.3.3 B: Relative risk of bruising at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	32.9	18.8-61.3
Classical (2d-7d)	27.6	11.1-74.5
Late (8d-6months)	3.4	1.8-5.9
Total	6.4	4.9-8.5

7.3.4 Incidence Rates of Umbilical Bleeding

The overall incidence rate of umbilical bleeding was 40.3 per 1000 infants in the total cohort. Bleeding at the site of the umbilicus was more commonly reported in both cohorts of infants, with overall incidence rates of 72.3 and 36.6 per 1000 infants (Table 7.3.4A) , and representing 35-40% of all reported bleeding symptoms in the deceased and survival cohorts of infants, respectively. The relative risks were 7.1 (95% CI 5.4-9.4), 2.8 (95% CI 2.2-3.5) and 1.9 (95% CI 1.2-2.7) in the deceased versus surviving cohorts for the early, classic and late stages, respectively, appearing to reflect a disproportionately higher risk of bleeding occurring in the first day of life among infants who did not survive (Table 7.3.4 B).

Table 7.3.4 A: Incidence rates of umbilical bleeding per 1000 infants at outset of specified age intervals

Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased Infants		Incidence of Bleeding in all Infants in Study Cohort	
Umbilical Bleeding	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	122	4.6	102	32.5	224	7.5
Classical (2d-7d)	468	17.5	94	46.6	562	19.6
Late (8d-6months)	372	13.9	31	25.9	403	14.4
Don't Know	15	0.6	0	0	15	0.5
Total	977	36.6	227	72.3	1204	40.3

Table 7.3.4 B: Relative risk of umbilical bleeding at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	7.1	5.4-9.4
Classical (2d-7d)	2.8	2.2-3.5
Late (8d-6months)	1.9	1.2-2.7
Total	1.9	1.7-2.3

7.3.5 Incidence Rates of Fresh Intestinal Bleeding (Red Blood in Stool)

The presence of bright red blood in stools was uniformly reported to be virtually non-existent in the first day of life in both cohorts, with reported incidence rates of 0.3 and 0.6 per 1000 in the surviving and deceased cohorts, respectively (Table 7.3.5A). Incidence rates in both the groups remained very low in the classic period (1.3 and 5.2 per 1000, respectively) but increased markedly after the first week of life (8 days to 6 months of age) to 26.4 and 30.1 per 1000 in the two respective cohorts, yielding relative risks of 1.9 (95% CI 0.2-9.1), 3.9 (95%CI 1.7-8.1) and 1.1 (95% CI 0.8-1.6) (Table 7.3.5B).

Table 7.3.5 A: Incidence rates of red blood in stool per 1000 infants at outset of specified age intervals

	Incidence of Bleeding among Surviving Infants		**Incidence of Bleeding among Deceased Infants**		**Incidence of Bleeding in all Infants in Study Cohort**	
Red Blood in Stool	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	9	0.3	2	0.6	11	0.4
Classical (2d-7d)	35	1.3	10	5.2	45	1.6
Late (8d-6months)	705	26.4	36	30.1	741	26.6
Don't Know	42	1.2	2	0.6	44	1.5
Total	791	29.6	50	15.9	841	28.2

Table 7.3.5 B Relative risk of red blood in stool at outset of specified age intervals

Age Intervals	**Relative Risk**	**95% Confidence Interval**
Early (<24 hours)	1.9	0.2-9.1
Classical (2d-7d)	3.9	1.7-8.1
Late (8d-6months)	1.1	0.8-1.6
Total	0.5	0.4-0.7

As suggested also in the proportionate ratio analysis, the extremely low rates in the first week of life, and comparable and much higher rates thereafter suggest that this symptom may be reflecting risk of dysenteric stools rather than an inherent bleeding disorder.

Importantly, the comparability of this symptom across both cohorts, unlike other highly fatal symptoms, supports an argument that recall may have been equally good in both groups of parents.

7.3.6 Incidence Rates of Dark Stool

Parental reporting of dark stools in infants could represent bleeding from the upper gastrointestinal tracts. The overall incidence rate of dark stool was 9.3 per 1000 infants (Table 7.3.6A). The relative risk was 2.4 (95% CI 1.7-3.2), reflecting greater risk of dark stool in the cohort of deceased infants than surviving infants. The relative risks were 12.9 (95% CI 7.4-22.3) and 3.7 (95% CI 2.3-5.5) among the deceased versus surviving infants' cohort for the classic and late stages, respectively (Table 7.3.6 B).

Table 7.3.6 A: Incidence rates of dark stool per 1000 infants at outset of specified age intervals

	Incidence of Bleeding among Surviving Infants		**Incidence of Bleeding among Deceased Infants**		**Incidence of Bleeding in all Infants in Study Cohort**	
Dark Stool	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	0	0	0	0	0	0
Classical (2d-7d)	30	1.1	28	14.5	58	2.0
Late (8d-6months)	171	6.4	28	23.4	199	7.1
Don't Know	16	0.6	4	1.3	20	0.7
Total	217	8.1	60	19.1	277	9.3

Table 7.3.6 B: Relative risk of dark stool at outset of specified age intervals

Age Intervals	**Relative Risk**	**95% Confidence Interval**
Early (<24 hours)		
Classical (2d-7d)	12.9	7.4-22.3
Late (8d-6months)	3.7	2.3-5.5
Total	2.4	1.7-3.2

Relative risk analysis revealed that upper gastrointestinal bleeding in the form of dark stool appeared to be a fatal risk for deceased infants especially during 2 to 7 days of life. The reporting of dark stool for the first two days after birth was not taken into account to avoid the possibility of meconium at birth being wrongly reported as dark stool.

7.3.7 Incidence Rates of Bulging Fontanel

Bulging fontanel is considered as one of the major symptoms of intracranial bleeding[12]. The overall incidence rate was 15.4 per 1000 infants in the total cohort of surviving and deceased infants. The incidence rates were 13 and 35.4 per 1000 infants among surviving and deceased infants, respectively (Table 7.3.7 A).

Table 7.3.7 A: Incidence rates of bulging fontanel per 1000 infants at outset of specified age intervals

	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased infants		Incidence of Bleeding in all Infants in Study Cohort	
Bulging Fontanel	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	41	1.5	40	12.7	81	2.7
Classical (2d-7d)	24	0.9	26	13.4	50	1.7
Late (8d-6months)	262	9.8	37	30.9	299	10.7
Don't Know	21	0.8	8	2.5	29	0.9
Total	348	13.0	111	35.4	459	15.4

Table 7.3.7 B: Relative Risk of bulging fontanel at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	8.3	5.2-13.2
Classical (2d-7d)	14.9	8.2-27.2
Late (8d-6months)	3.2	2.2-4.5
Total	2.7	2.2-4.5

The overall relative risk was 2.7 (95% CI 2.2-3.4) reflecting greater risk of bulging fontanel in cohort of infants who died by 6 months of age than surviving infants.

The relative risks were 8.3 (5.2-13.2), 14.9 (95% CI 8.2-27.2) and 3.2(95% CI 2.2-4.5) in the deceased versus surviving infants' cohort for the early, classic and late stages, reflecting a higher risk of bulging fontanel occurring during early and classic stages (i.e. within 7 days of life) among the deceased infants (Table 7.3.7 B).

7.3.8 Incidence Rates of any Nasal Bleeding or Bruising

The overall incidence rates of any nasal bleeding or bruising were 8.3 and 92.1 per 1000 infants among surviving and deceased infants, respectively (Table 7.3.8A). The relative risk was 11.1 (95% CI 9.2-13.3) reflecting greater risk in the cohort of infants who died by 6 months of age than surviving infants.

Table 7.3 8 A : Incidence rates of any nasal bleeding or bruising per 1000 infants at outset of specified age intervals

Combination of Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased Infants		Incidence of Bleeding in all Infants in Study Cohort	
	n	Incidence	n	Incidence	n	Incidence
Any Nasal Bleeding or Bruising						
Early (<24 hours)	18	0.7	136	43.3	154	5.2
Classical (2d-7d)	17	0.6	96	49.6	113	3.9
Late (8d-6months)	180	6.7	53	44.2	233	8.6
Don't Know	7	0.3	4	1.3	11	0.4
Total	222	8.3	289	92.1	511	17.1

Table 7.3.8 B: Relative risk of any nasal bleeding or bruising at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	64.3	39.1-111.8
Classical (2d-7d)	77.9	46.1-139.4
Late (8d-6months)	6.6	4.7-9.0
Total	11.1	9.2-13.3

The relative risks were 64.3 (95% CI 39.1-111.8), 77.9 (95% CI 46.1-139.4) and 6.6 (95% CI 4.7-9.0) in the deceased versus surviving infants' cohort for the early, classic and late stages, respectively (Table 7.3.8 B). The relative risk analysis reflected a higher risk of nasal bleeding or bruising occurring during early and classic stages (i.e. within 7 days of live) among the deceased infants.

7.3.9 Incidence Rates of any Nasal Bleeding or Bulging Fontanel

The overall incidence rate of any nasal bleeding or bulging fontanel was 24.7 per 1000 infants in the total cohort of surviving and deceased infants (Table 7.3.9A). The relative risk of any nasal bleeding or bulging fontanel was 5.8 (95% CI 4.9-6.8), reflecting 5.8 times greater risk in the cohort of infants who died by 6 months of age than surviving infants (Table 7.3.9 B).

Table 7.3.9 A: Incidence rates of any nasal bleeding or bulging fontanel per 1000 infants at outset of specified age intervals

Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased Infants		Incidence of Bleeding in all Infants in Study Cohort	
Any Nasal Bleeding or Bulging Fontanel	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	43	1.6	113	36.0	156	5.2
Classical (2d-7d)	33	1.2	104	53.7	137	4.8
Late (8d-6months)	339	12.7	73	60.9	412	14.8
Don't Know	23	0.9	10	3.2	33	1.1
Total	438	16.4	300	95.6	738	24.7

Table 7.3.9 B: Relative risk of nasal bleeding or bulging fontanel at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	22.4	15.6-32.6
Classical (2d-7d)	43.5	29.0-66.6
Late (8d-6months)	4.8	3.7-6.2
Total	5.8	4.9-6.8

Relative risks were 22.5 (95% CI 15.6-32.6), 43.5 (95% CI 29.0-66.6) and 4.8 (95% CI 3.7-6.2) in the deceased versus surviving infants' cohort for the early, classic and late stages, reflecting a higher risk of this combination of bleeding occurring during early and classic stages (within 7 days of live) among the deceased infants.

7.3.10 Incidence Rate of any Nasal Bleeding or Bruising or Umbilical Bleeding

The overall incidence rate of any nasal bleeding or bruising or umbilical bleeding was 56.1 per 1000 infants in the total cohort of surviving and deceased infants (Table 7.3.10A).

Table 7.3.10 A: Incidence rates of any nasal bleeding or bruising or umbilical bleeding per 1000 infants at outset of specified age intervals

Symptoms	Incidence of Bleeding among Surviving Infants		Incidence of Bleeding among Deceased Infants		Incidence of Bleeding in all Infants in Study Cohort	
Any Nasal Bleeding or Bruising or Umbilical Bleeding	n	Incidence	n	Incidence	n	Incidence
Early (<24 hours)	137	5.1	223	71.0	360	12.1
Classical (2d-7d)	478	17.9	171	88.3	649	22.7
Late (8d-6months)	546	20.5	78	65.1	624	22.4
Don't Know	30	1.1	12	3.8	42	1.4
Total	1191	44.6	484	154.2	1675	56.1

Table 7.3. 10 B: Relative risk of any nasal bleeding or bruising or umbilical bleeding at outset of specified age intervals

Age Intervals	Relative Risk	95% Confidence Interval
Early (<24 hours)	13.8	11.1-17.3
Classical (2d-7d)	4.9	4.1-5.9
Late (8d-6months)	3.2	2.5-4.1
Total	3.5	3.1-3.9

The relative risk of any nasal bleeding or bruising or umbilical bleeding was 3.5 (95% CI 3.1-3.9), reflecting 3.5 times greater risk in the cohort of infants who died by 6 months of age than surviving infants. The relative risks were 13.8 (95% CI 11.1-17.3), 4.9 (95%CI 4.1-5.9) and 3.2 (95% CI 2.5-4.1) in the deceased versus surviving infants' cohort for the early, classic and late stages, reflecting a higher risk of any nasal bleeding or bruising or umbilical bleeding occurring during first day of life among the deceased infants (Table 7.3.10 B).

7.4 Mean and Median Time to Death from Bleeding Symptoms

Median (with interquartile range, or IQR) and mean (with standard deviation) time intervals to death for infants with bleeding histories have also been calculated from the age at which each bleeding symptom was reported within the three classical bleeding periods. The median time to death was 1 day (IQR: also the same 1st day) for early onset (<24 hours) of nasal bleeding, 1 day for bruising (IQR: 0 to 1 day), 1 day for umbilical bleeding (IQR: 0 to 2 days), and 1 day (IQR: 0 to 2.5 days) for bulging fontanel, indicating that ~75% of infants in this special cohort died within the 1st 1-2 days of the day on which the reported symptom occurred. The median time to death for early onset (<24 hours) of red blood in stool was 4.5 days (IQR: 3 to 6 days). The median time to death was 2 days (IQR: 2 to 3 days) for classic onset (2 to 7 days) and 17 days (IQR: 11 to 48.5 days) for late onset (8 days -6 mo) nasal bleeding. Similarly, infants in the deceased cohort who had bruising and bulging fontanel within 2 days to 7 days of age, half of them died within 5 days of their life. The median time to death was 27 day for classic onset and 76.5 days for late onset of red blood in stool, which supported the earlier interpretation of the likelihood of this bleeding being due to dysentery.

Table 7.4: Mean and median time to death from the interval at which a bleeding symptom was reported for the cohort of deceased infants

Bleeding Symptoms	Time of Death				
	Mean (in days)	Median (in days)	Inter-quartile Range (25%-75%)	SD (±)	95% CI of Mean
Any Bleeding					
Early (<24 hours)	3.17	1	0-2	10.51	1.86-4.47
Classical (2d-7d)	11.76	4	2-12.5	19.29	9.20-14.33
Late (8d-6months)	61.31	45.5	17-85.5	51.89	53.20-69.41
Nasal Bleeding					
Early (<24 hours)	1.84	1	1-1	4.69	0.80-2.88
Classical (2d-7d)	4.01	2	2-3	5.96	2.70-5.32
Late (8d-6months)	36.6	17	11-48.5	38.46	24.32-48.93
Bruising					
Early (<24 hours)	1.10	1	0-1	2.90	0.36-1.83
Classical (2d-7d)	8.5	4.5	3-8	11.17	2.55-14.45
Late (8d-6months)	61.4	28	19-129	55.8	30.49-92.32
Umbilical Bleeding					
Early (<24 hours)	5.19	1	0-2	14.56	0.36-8.06
Classical (2d-7d)	17.5	10	3-21	24.09	2.55-14.45
Late (8d-6months)	36.8	22	13-48	37.15	30.49-92.32
Red Blood in Stool					
Early (<24 hours)	4.5	4.5	3-6	2.12	-14.56-23.56
Classical (2d-7d)	32.8	27	4-69	28.38	12.49-53.11
Late (8d-6months)	86.78	76.5	54.5-109.5	51.86	69.23-104.33
Dark Stool					
Early (<24 hours)	-	-	-	-	-
Classical (2d-7d)	9.29	7	5-9	8.54	5.97-12.59
Late (8d-6months)	68.61	51.5	22.5-98.5	55.06	47.26-89.96
Bulging Fontanel					
Early (<24 hours)	5.67	1	0-2.5	13.60	1.33-10.03
Classical (2d-7d)	11.81	4.5	3-14	14.59	5.91-17.70
Late (8d-6months)	89.68	82	49-135	50.69	72.78-106.58
Nasal Bleeding or Bruising					
Early (<24 hours)	1.51	1	0-1	4.10	0.82-2.21
Classical (2d-7d)	4.74	2	2-4.5	7.26	3.27-6.21
Late (8d-6months)	41.02	20	12-53	43.59	29.00-53.03

Continuation of Table 7.4:

	Mean (in days)	Median (in days)	Inter-quartile Range (25%-75%)	SD (±)	95% CI of Mean
Nasal Bleeding or Bulging Fontanel					
Early (<24 hours)	2.96	1	0-2	8.77	1.33-4.59
Classical (2d-7d)	6.03	3	2-5.5	9.52	4.18-7.88
Late (8d-6months)	60.09	45	14-91	51.71	48.03-72.16
Nasal or Bruising or Umbilical Bleeding					
Early (<24 hours)	2.99	1	0-1	10.24	1.64-4.35
Classical (2d-7d)	11.26	3	2-12	19.51	8.31-14.20
Late (8d-6months)	40.37	21	12-51	42.26	30.84-49.89

7.5 Case Fatality Rates of Bleeding Symptoms

Case fatality rates were calculated as a measure of severity of bleeding symptoms among the infants born in the study area. By text book definition[69], the numerator of a case-fatality rate should be restricted to the deaths among individuals who are defined as cases of a disease. Although it was not possible to distinguish between the deaths due to bleeding and deaths from other causes in the analysis, it was assumed, based on time-to-death data presented in the preceding section, that bleeding when present might have contributed to death in many instances, thus providing a basis for estimating case fatality rates of bleeding symptoms in this study.

For calculating any specific case fatality rate, the numerator was deceased infants with that specific bleeding symptom and the denominator was the sum of the numbers of infants in both the deceased and surviving cohorts reported to have had that specific bleeding symptom.

Case fatality rates were calculated along with their 95% CI for individual bleeding symptoms; e.g. nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding, dark stool, bulging fontanel and for combined bleeding symptoms as a way to explore their joint effects on fatality risk; e.g. any nasal or bruising, any nasal or bulging fontal, any nasal or bruising or umbilical and any of bleeding symptoms based on the time of onset (early, classical and late, as defined earlier).

7.5.1 Case Fatality Rates of Individual Bleeding Symptoms

The case fatality rate for any bleeding symptom was 21.3% (95% CI 19.8-22.8). When the case fatality rates were calculated based on the time of onset of bleeding, the highest 58.7% (95% CI 54.0-63.3) was for early onset followed by classic onset 29.7% (95% CI 26.4-32.9) and late onset 9.1% (95% CI 7.8-10.5).

The over all case fatality rate of nasal bleeding was 68.3% (95% CI 63.0-73.6). The case fatality rate was highest for the early onset nasal bleeding (97.6%, 95% CI 94.3-99.8) followed by classical (90.1%, 95% CI 83.9-96.3) and late onset (33.1, 95% CI 24.7-41.5). Extremely high case fatality rates were found for early and classic onset of nasal bleeding, and 95% CI for both the rates were statistically significant (Table 7.5.1).

The overall case fatality rate for bruising was 43.0% (95% CI 36.5-49.5). The case fatality rate was highest for early onset (79.5%, 95% CI 70.5-88.5) followed by classical (66.7%, 95% CI 47.4-85.9) and late onset (13.2%, 95% CI 7.0-19.4) of bruising. The over all case fatality rate for umbilical bleeding was 18.9% (95% CI 16.7-21.1).

Table 7.5.1: Case fatality rates of individual bleeding symptoms with 95% CI

	Total	Survived infants	Deceased infants	Case Fatality Rates	95% CI
Nasal Bleeding	300	95	205	68.3	63.0-73.6
Early (<24 hours)	83	2	81	97.6	94.3-99.8
Classical (2d-7d)	91	9	82	90.1	83.9-96.3
Late (8d-6months)	121	81	40	33.1	24.7-41.5
Don't Know	5	3	2		
Bruising	223	127	96	43.0	36.5-49.5
Early (<24 hours)	78	16	62	79.5	70.5-88.5
Classical (2d-7d)	24	8	16	66.7	47.4-85.9
Late (8d-6months)	114	99	15	13.2	7.0-19.4
Don't Know	7	4	3		
Umbilical Bleeding	1204	977	227	18.9	16.7-21.1
Early (<24 hours)	224	122	102	45.5	38.9-52.0
Classical (2d-7d)	562	468	94	16.7	13.6-19.8
Late (8d-6months)	403	372	31	7.7	5.1-10.3
Don't Know	15	15	0		
Fresh Intestinal Bleeding	841	791	50	5.9	4.3-7.5
Early (<24 hours)	11	9	2	18.2	-5.7-42.1
Classical (2d-7d)	45	35	10	22.2	9.9-34.5
Late (8d-6months)	741	705	36	4.9	3.3-6.5
Don't Know	44	42	2		
Dark Stool	277	217	60	21.7	19.2-24.2
Early (<24 hours)	0	0	0	0	
Classical (2d-7d)	58	30	28	48.3	35.3-61.3
Late (8d-6months)	199	171	28	14.1	9.3-18.9
Don't Know	20	16	4		
Bulging Fontanel	459	348	111	24.2	22.2-26.2
Early (<24 hours)	81	41	40	49.4	38.4-60.4
Classical (2d-7d)	50	24	26	52.0	38.0-65.9
Late (8d-6months)	299	262	37	12.4	8.7-16.1
Don't Know	29	21	8		

The case fatality rate was highest for early onset (45.5%, 95% CI 38.9-52.0) of umbilical bleeding. The case fatality rate for fresh intestinal bleeding was 15.9% (95% CI 4.3-7.5) with the highest case fatality for classical onset (22.2%, 95% CI 9.9-34.5).

The case fatality rate for dark stools was 21.7% (95% CI 19.2-24.2). When case fatality rates of dark stool were calculated based on time of onset of bleeding, the case fatality rate was highest for classical onset (48.3%, 95% CI 35.3-61.3) followed by late on set (14.1%, 95% CI 9.3-18.9). Bulging fontanel can be a manifestation of intracranial bleeding[12], although more often it is considered to reflect benign intracranial volume expansion, with or without any increase in intracranial pressure[73]. The over all case fatality rate for bulging fontanel was, therefore expectedly lower, at 24.2% (95% CI 22.2-26.2), with risk being highest for classical (52.0%, 95% CI 38.0-65.9) followed by early (49.4%, 95% CI 38.4-60.4) and late (12.4%, 95% CI 8.7-16.1) onsets.

7.5.2 Caste Fatality Rates of Combination of Bleeding Symptoms

Case fatality rates were also calculated for combinations of nasal bleeding or bruising, nasal bleeding or bulging fontanel, and any of nasal bleeding, bruising or umbilical bleeding with their 95% confidence intervals (Table 7.5.2). The highest case fatality rate of 56.6% was observed for nasal bleeding or bruising (95% CI 52.3-60.9), with the highest rates observed for early and classical onsets: 88% (95% CI 83.2-93.4) and 85% (95% CI 78.3-9.15), respectively.

Table 7.5.2: Case fatality rates of combination of bleeding symptoms with 95% CI

	Total	Surviving Infants	Deceased Infants	CFR	95% CI
Any Nasal Bleeding/ Bruising	511	222	289	56.6	52.3-60.9
Early (<24 hours)	154	18	136	88.3	83.2-93.4
Classical (2d-7d)	113	17	96	84.9	78.3-91.5
Late (8d-6months)	233	180	53	22.7	17.3-28.1
Don't Know	11	7	4		
Any Nasal / Bulging Fontanel	738	438	300	40.7	37.2-44.2
Early (<24 hours)	156	43	113	72.4	65.4-79.4
Classical (2d-7d)	137	33	104	75.9	68.7-83.1
Late (8d-6months)	412	339	73	17.7	4.5-30.9
Don't Know	33	23	10		
Any Nasal/ Bruising /Umb. Bleeding	1675	1191	484	28.9	26.7-31.1
Early (<24 hours)	360	137	223	61.9	56.8-66.9
Classical (2d-7d)	649	478	171	26.3	22.9-29.7
Late (8d-6months)	624	546	78	12.5	9.9-15.1
Don't Know	42	30	12		
Any Bleeding	3045	2395	650	21.3	19.8-22.8
Early (<24 hours)	429	177	252	58.7	54.0-63.3
Classical (2d-7d)	744	524	220	29.6	26.4-32.9
Late (8d-6months)	1757	1597	160	9.1	7.8-10.5
Don't Know	115	97	18		

The case fatality rate for any nasal bleeding or bulging fontanel was 40.7% (95% CI 37.2-44.2). Similar to nasal bleeding or bruising, case fatality rates for nasal bleeding or bulging fontanel combined was also high for early (72.4% 95% CI 65.4-79.4) and classic (75.9% 95% CI 68.7-83.1) onsets. Overall case fatality rate was comparatively lower for any nasal or bruising or umbilical bleeding 28.9% (95% CI 26.7-31.1). Although early onset of any nasal or bruising or umbilical bleeding was quite high (61.9%, 95% CI 56.8-66.9).

7.6 Summary Findings

In this chapter, estimates of age interval-specific mortality rates, proportionate distributions of the bleeding symptoms, incidence rates per 1000 infants as well as case fatality rates with 95% CI for bleeding symptoms have been reported based on their age of onset i.e., early (<24 hours), classical (2 days-7 days) and late (8 days-6months).

The total numbers of live births in this analytic cohort was 29,844 at the outset among whom 26,705 infants survived and 3,139 died by six months of age. A total of 1941 infants died within 7 days of birth resulting in a neonatal mortality rate 65.0 in 1000 live births. The cumulative mortality rate of infants up to 6 months of age was 105.2 in 1000 live births.

Among 26,705 infants who survived up to 6 months of age, 2395 (9.0%) were reported by parents to have had at least one bleeding symptom up to that age. In contrast, among 3,139 infants who died by 6 months of age (the deceased cohort) 650 (20.7%) were reported to have had bleeding symptoms prior to death, reflecting a frequency that was 2.3 times greater than surviving infants. Overall, higher percentages of deceased infants had nasal bleeding (31.5% vs. 4%), bruising (14.8% vs. 5.3%) and bulging fontanel (17.1% vs. 14.5%) than surviving infants. On the other hand, higher percentages of surviving infants had umbilical bleeding (40.8% vs. 34.9%) and red blood in stools (33.0% vs. 7.7%) than deceased infants, reflecting a tendency for these symptoms to arise post-neonatally and the fact that fewer infants in the deceased cohort lived long enough to have those symptoms.

The incidence rates of nasal bleeding were 3.6 and 65.3 per 1000 infants among surviving and deceased infants, respectively. Nasal bleeding occurring in the first day of life occurred virtually only in infants who died, with a relative risk being 344.6 (95% CI 92.3-2893.4), 125.8 (95%CI 62.9-284.8) and 11.1 (95% CI 7.3-16.3) during the early, classic and late periods respectively, compared to the survivors.

The overall incidence rates of bruising were 4.8 and 30.6 per 1000 infants among surviving and deceased infants respectively, revealing 6.4 (95% CI 4.9-8.5) times greater risk in the cohort of infants who died by six months of age. Bleeding at the site of the umbilicus was more commonly reported in both cohorts of infants, with overall rates of 36.6 and 72.3 per 1000 infants among surviving and deceased cohorts, respectively.

The incidence rates of presence of bright red blood in stools remained very low in the classic period (1.3 and 5.2 per 1000, respectively) but increased markedly in both groups of infants after the first week of life (8 days to 6 months of age) to 26.4 and 30.1 per 1000 infants in the two respective cohorts. The overall incidence rates of dark stool were 8.1 and 19.1 per 1000 infants among surviving and deceased infants respectively. The relative risk of dark stool for classic onset was 12.9 (95% CI 7.4-22.3) reflecting a much higher risk among the deceased infants.

The incidence rate of bulging fontanel was 13 and 35.4 per 1000 infants among the cohort of surviving and deceased infants, respectively. The relative risk was 2.7 (95% CI 2.2-3.4) times greater in cohort of infants who died by 6 months of age than surviving infants.

Relative risks were higher for early (8.3, 95% CI 5.2-13.2) and classic onset (14.9, 95% CI 8.2-27.2), reflecting a higher risk of bulging fontanel occurring during first week of life among the cohort of deceased infants.

Very high case fatality rates were found for early onset nasal bleeding (97.6%, 95% CI 94.3-100.9) and classic onset nasal bleeding (90.1%, 95% CI 83.9-96.3). High case fatality rates were also found to be associated with early onset (79.5%, 95% CI 70.5-88.5) bruising and classic onset (66.7%, 95% CI 47.4-85.9) bruising. Case fatality rates were also very high for any nasal bleeding or bruising (88% and 85%) and any nasal bleeding or bulging fontanel (72.4% and 75.9%) for the early and classical onset, respectively.

Chapter 8. Breastfeeding and Infantile Bleeding

Given the importance of breastfeeding in the literature as a potential causal determinant of bleeding related to vitamin K deficiency in early life[3-5,10,11,23,42], analyses of the infantile bleeding status were done with patterns of breastfeeding in both cohorts of surviving and deceased infants separately. The direction and strength of association between exclusive breastfeeding and risk of individual bleeding and combination of bleeding symptoms were also analyzed, based on age of onset for both surviving and deceased infants separately. Similar analyses with colostrum feeding are also presented in this chapter.

8.1 Prevalence of Breastfeeding among Cohort of Surviving Infants

When colostrum feeding status among cohort of surviving infants was analyzed, it was revealed that about 95% of both types of infants were fed colostrum. The mean initiation time of breastfeeding was 32.7 ± 28.4 hours for infants who had bleeding and 31.9 ± 28.1 hours for infants who did not have bleeding. Majority of both types of infants who had (99.1%) and who did not have (99.4%) bleeding in the surviving cohort were breastfeeding at 6 months of age.

Table 8.1: Prevalence of breastfeeding among cohort of surviving infants

	Infants who had bleeding n= 2385		Infants who did not have bleeding n= 24074		Total n=26459	
Colostrum Fed	**n=2379**	**%**	**n=24041**	**%**	**n=26420**	**%**
No	121	5.1	1188	4.9	1309	4.69
Yes	2257	94.9	22816	94.9	25073	94.9
Don't know	1	0.04	37	0.2	38	0.2
Pearson Chi^2 (2) = 1.9752					*p-value 0.372*	
Breastfeeding Initiation Time (in hours)	**n=2379**	**%**	**n=24039**	**%**	**n=26418**	**%**
Immediate	91	3.8	1013	4.2	1104	4.2
1-2	185	7.8	2178	9.1	2363	8.9
3-6	249	10.5	2277	9.5	2526	9.6
7-12	341	14.3	3216	13.4	3557	13.5
13-24	316	13.3	3433	14.3	3749	14.2
25-98	1080	45.4	10700	44.5	11782	44.5
Don't know	115	4.8	1222	5.1	1337	5.1
Pearson Chi^2= (6) = 10.9871					*p-value 0.202*	
Mean(hours)	32.7		31.9		32.1	
Median(hours)	24		24		24	
SD ±	28.4		28.1		28.1	
t-test	*t= -1.1131*				*p-value 0.2657*	
Breastfeeding at 6 mo of Age	**n= 2395**	**%**	**n=24028**	**%**	**n=26423**	**%**
No	21	0.9	154	0.6	175	0.7
Yes	2374	99.1	23872	99.4	26246	99.3
Don't know			2	0.01	2	0.1
Pearson Chi^2(2) = 2.0408					*p-value 0.360*	

8.2 Prevalence of Exclusive Breastfeeding among Cohort of Surviving Infants

Exclusive breastfeeding (EBF) among the cohort of surviving infants was ascertained by combining data from historic questions posed to mothers at six months follow up visits about whether the infant was breast-fed and the timing of introducing a list of common complementary foods.

Table 8.2: Prevalence of exclusive breastfeeding among cohort of surviving infants

Exclusively Breastfed	**Infants who had bleeding n=2395**		**Infants who did not have bleeding n=24310**		**Total n=26705**	
< 24 hours	**n=177**	**%**	**n=26528**	**%**	**n=26705**	**%**
No	108	61.0	15188	57.3	15296	57.3
Yes	69	39.0	11340	42.7	11409	42.7
Pearson $Chi^2(1)$= 1.0181						*p-value 0.313*
2-7 days	**n=524**	**%**	**n=26181**	**%**	**n=26705**	**%**
No	305	58.2	15708	60.0	16013	60.0
Yes	219	41.8	10473	40.10	10692	40.0
Pearson Chi^2 (1) = 0.6868						*p-value 0.407*
8d-3mo	**n= 625**	**%**	**n= 26080**	**%**	**n=26705**	**%**
No	421	67.4	18355	70.4	18776	70.3
Yes	204	32.6	7725	29.6	7929	29.7
Chi^2 (1) = 2.6660						*p-value 0.103*
3m-6mo	**n= 972**	**%**	**n=25733**	**%**	**n=26705**	**%**
No	838	86.2	21399	83.2	22237	83.3
Yes	134	13.8	4334	16.8	4468	16.7
$Chi^2(1)$ = 6.2794						*p-value 0.012*

Infants reported to have been breastfed at a specific age and who also had no history of receiving other foods before or at any time during the specific age interval were classified as being exclusively breastfed at that age interval. That is, classification of infants as EBF was conditional on being breast fed exclusively at the age being considered and all prior age intervals.

When EBF rates among the cohort of surviving infants were verified, 42.7% were exclusive breastfed in the first day of life, 40% at 2 to 7 days of age, 29.7% at 8 days to 3 months of age and 16.7% at 3 month to 6 months of age (Table 8.2). In the first day of life 39% of surviving infants who had a history of bleeding and 42.7% of infants who did not have such history had been exclusively breastfed. At 2 days to 7 days of life around 42% of infants who had bleeding and 40% of infants who did not have bleeding were exclusively breastfed.

At 8 days to 3 months of age higher percentage of infants who had bleeding were exclusively breastfed than infants who did not have bleeding (32.6% vs. 29.6%), but the difference was not statistically significant (p= 0.103). At 3 months to 6 months age, a higher percentage (p= <0.01) of infants who did not have bleeding than infants who had bleeding was exclusively breastfed (16.8% vs. 13.8%, respectively).

8.3 Prevalence of Breastfeeding among Cohort of Deceased Infants

When colostrum feeding status among the cohort of deceased infants was analyzed, in general, 90.6% of deceased infants had been fed colostrum; ~ 92% for infants who had bleeding compared to 90% of infants who did not have bleeding.

Table 8.3: Prevalence of breastfeeding among cohort of deceased infants

	Infants who had bleeding n= 650		**Infants who did not have bleeding n= 2439**		**Total n=3089**	
Colostrum Fed	**n=409**	**%**	**n=1338**	**%**	**n=1747**	**%**
No	32	7.8	123	9.2	155	8.9
Yes	377	92.2	1206	90.1	1583	90.6
Don't know	0	0	9	0.7	9	0.5
Pearson Chi^2=(2) =	*3.5568*				*p-value 0.169*	
Breastfeeding Initiation Time (in hours)	**n= 409**	**%**	**n= 1338**	**%**	**n=1747**	**%**
Immediate	19	4.7	54	4.0	73	4.2
1-2	46	11.3	147	10.9	193	11.1
3-6	52	12.7	134	10.0	186	10.7
7-12	57	13.9	186	13.9	243	13.9
13-24	50	12.2	178	13.3	228	13.1
25-98	158	38.6	529	39.5	687	39.2
Don't know	27	6.6	110	8.2	137	7.8
Pearson Chi^2 (6) =	*3.8338*				*p-value 0.699*	
Mean (hours)	28.2		30.8		30.2	
Median (hours)	17		24		23	
SD ±	27.4		28.3		28.1	
t-test	*t=1.6054*				*p-value 0.1086*	
Breastfeeding before Death	**n=406**	**%**	**n=1338**	**%**	**n=1747**	**%**
No	26	6.4	98	7.3	124	7.1
Yes	383	93.6	1238	92.5	1621	92.8
Don't know	0	0	2	0.2	2	0.1
Pearson Chi^2= (2)=	*1.0665*				*p-value 0.587*	

The mean initiating time of breastfeeding among infants in this cohort who had died was 28.2 ± 27.4 hours compared to 30.8 ±28.3 hours in infants who had no bleeding history, suggesting that the deceased infants who had bled initiated breastfeeding slightly earlier than deceased infants who did not have any history of bleeding, although the difference was not statistically significant (p=0.1086).

8.4 Prevalence of Exclusive Breastfeeding among Cohort of Deceased Infants

Exclusive breastfeeding (EBF) for the cohort of deceased infants was defined in a similar way as to survivors by combining data from historic questions posed to mothers during verbal autopsy interviews about whether the infant had been breastfed and the timing of introducing a list of common complementary foods.

Table 8.4: Prevalence of exclusive breastfeeding among cohort of deceased infants

Exclusive Breastfeeding	**Infants who had bleeding n= 650**		**Infants who did not have bleeding n=2489**		**Total n=3139**	
< 24 hours	**n=252**	**%**	**n=2887**	**%**	**n=3139**	**%**
No	218	86.5	2267	78.5	2485	79.2
Yes	34	13.5	620	21.5	654	20.8
Pearson Chi²(1)= 8.9562					*p-value 0.003*	
2-7 days	**n=220**	**%**	**n=2919**	**%**	**n=3139**	**%**
No	163	74.1	2416	82.8	2579	82.2
Yes	57	25.9	503	17.2	560	17.8
Pearson Chi² (1) = 10.5091					*p-value 0.001*	
8d-3mo	**n= 139**	**%**	**n= 3000**	**%**	**n=3139**	**%**
No	118	84.9	2536	84.5	2653	84.5
Yes	21	15.1	465	15.5	486	15.5
Pearson Chi² (1) = 0.0156					*p-value 0.901*	
3m-6mo	**n= 21**	**%**	**n=3118**	**%**	**n=3139**	
No	20	95.2	2641	84.7	2661	84.8
Yes	1	4.8	477	15.3	478	15.2
Pearson Chi²(1) = 1.7939					*p-value 0.180*	

Infants reported to have been breastfed at a specific age and who also had no history of receiving other foods before or at any time during the specific age interval were classified as having been exclusively breastfed in that age interval. That is, classification of infants as EBF was conditional on being breast fed exclusively at the age being considered and all prior age intervals.

On examination, 20.8% had been exclusively breastfed in the first day of life, 17.8% at 2 days to 7 days of age, 15.5% at 8 days to 3months of age and 15.2% at 3 months to 6 months of age (Table 8.4). Twenty one percent of deceased infants who had not bled and 13% of the cohort who had bled had been exclusively breastfed in the first day of life (p= <0.005). On the other hand, significantly higher percentage of infants who had bleeding (25.9%) were on exclusive breastfeeding than infants who did not have bleeding (17.2%) at 2 days to 7 days of age (p=<0.001) among the cohort of deceased infants. Exclusive breastfeeding rates were similar for 8 days to 3 months for both infants who had and did not have bleeding (15.1% vs. 15.5%) among deceased infants.

8.5 Association between Exclusive Breastfeeding and Bleeding Status among Cohort of Surviving Infants

The relationships between exclusive breastfeeding and risk of individual and combined bleeding symptoms were examined among the cohort of surviving infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Crude and adjusted odds ratios with 95% CI were calculated to assess the association between EBF status and onset of bleeding at each sequential age as < 24hours (1st day), 2 days to 7 days, 8 days to 3 months and 3 months to 6 months (Table 8.5).

The odds ratios of EBF were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, morbidities, maternal age, maternal parity, obstructed delivery and religion. The adjusted odds of nasal bleeding associated with EBF relative to not EBF was 1.65 (95% CI 0.10-27.09) in the 1st day of life, 1.17 (95% CI 0.31-4.37) at 2 days to 7 days of age and 1.28 (95% CI 0.48-3.45)) at 8 days to 3 months of age (Table 8.5). The adjusted odds ratios were similar in direction and magnitude for age 1st day to 3 months (i.e., 1.17 to 1.65), reflecting a 17% to 65% higher risk of nasal bleeding associated with exclusive breast feeding, although, all 95% confidence intervals included unity. This analysis suggests EBF through the first 3 months of life could have been modestly associated with a higher risk of bleeding from nose compared to a feeding pattern that included early complementary foods during this time period.

The adjusted odds of bruising if EBF relative to not EBF was 1.36 (95% CI 0.49-3.81) in the 1st day of life, 2.48 (95% CI 0.59-10.42) at 2 days to 7 days of age and 1.31 (95% CI 0.69-2.49) at 3 months to 6 months of age. These adjusted odds ratios were similar in direction and magnitude for all these 3 age intervals with the highest risk being observed at 2 days to 7 days, during which EBF infants were ~2.5 times in higher risk of bruising; the association was weak, although not statistically significant (95% CI 0.59-10.42).

While the association with umbilical bleeding were examined; exclusive breastfeeding was found to be significantly associated with a 39% higher risk (adjusted OR= 1.39, 95% CI 1.11-1.73) at 8 days to 3 months of age compared to non-exclusive breastfeeding during this time period.

The adjusted odds for fresh intestinal bleeding for EBF was 0.44 (95% CI 0.09-2.18) in the 1st day of life, 1.17 (95% CI 0.58- 2.34) at 2-7 days, 0.95 (95% CI 0.64-1.41) at 8 days to 3 moths of age. In the crude analysis, exclusive breastfeeding at 3 months to 6 months of age appeared to be significantly associated with a 25% reduction of fresh intestinal bleeding, possibly reflecting a well known protective association of breastfeeding against dysentery. When the odds ratio was adjusted the association became non-significant (adjusted OR=1.13, 95% CI 0.84-1.51).

When similar analysis was done for combination of bleeding, it was found that the adjusted odds of either nasal bleeding or bruising if exclusively breast fed relative to if not exclusively breast fed was 1.39 (95% CI 0.53-3.67) in the first day of life, 1.66 (95% CI 0.64-4.31) at 2-7 days of age, 1.16 (95% CI 0.65-2.08) at 8 days to 3 months of age and 1.09 (95% CI 0.68-1.76) for 3 months to 6 months of age (Table 8.5). The direction and magnitude of the odds ratios were consistently similar across all age intervals for this combination of nasal bleeding and bruising, reflecting 9- 66% of higher risk of any nasal bleeding or bruising associated with exclusive breastfeeding for these age intervals, although 95% confidence intervals were not statistically significant.

Table 8.5: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to EBF among surviving infants

Exclusive Breastfeeding	Nasal Bleeding					Bruising					Umbilical Bleeding					Fresh Intestinal Bleeding				
			Crude		Adjusted			Crude		Adjusted			Crude		Adjusted			Crude		Adjusted	
	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI
1st day(<24 hr)	No	Yes					No	Yes					No	Yes					No	Yes				
No	15295	1	1				15287	9	1				15222	74	1				15289	7	1			
Yes	11408	1	1.34	0.02-105.15	1.65	0.10-27.09	11402	7	1.04	0.33-3.15	1.36	0.49-3.81	11361	48	0.87	0.59-1.27	0.91	0.63-1.32	11407	2	0.38	0.04-2.01	0.44	0.09-2.18
2-7 days																								
No	16008	5					16010	3					15739	274					15992	21				
Yes	10688	4	1.19	0.24-5.57	1.17	0.31-4.37	10687	5	2.49	0.49-16.08	2.48	0.59-10.42	10498	194	1.06	0.88-1.28	1.03	0.85-1.24	10678	14	0.99	0.47-2.06	1.17	0.58-2.33
8d-3mo																								
No	18764	12					18750	26					18544	232					18676	100				
Yes	7922	7	1.38	0.46-3.81	1.28	0.48-3.45	7918	11	1.00	0.45-2.09	1.16	0.56-2.37	7795	134	1.37	1.10-1.71	1.39	1.11-1.73	7894	35	0.83	0.55-1.23	0.95	0.64-1.41
3m-6mo																								
No	22185	52	0.96	0.43-1.91	0.90	0.44-1.84	22187	50					22232	5					21742	495				
Yes	4458	10					4456	12	1.19	0.58-2.28	1.31	0.69-2.49	4467	1	0.99	0.12-8.89	1.20	0.14-10.46	4393	75	0.75	0.58-0.96	1.13	0.84-1.51

Exclusive Breastfeeding	Nasal Bleeding /Bruising					Nasal Bleeding/ Bulging fontanel					Nasal Bleeding/ bruising/ Umbilical bleeding					Any Bleeding				
	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI
1st day (<24hr)	No	Yes					No	Yes					No	Yes					No	Yes				
No	15286	10	1				15267	29	1				15214	82	1				15188	108	1			
Yes	11401	8	1.07	0.37-3.02	1.39	0.53-3.67	11395	14	0.67	0.35-1.26	0.67	0.35-1.27	11354	55	0.90	0.63-1.28	0.97	0.66-1.37	11340	69	0.85	0.62-1.17	0.89	0.65-1.21
2-7 days																								
No	16005	8					15994	19					15734	279					15708	305				
Yes	10683	9	1.68	0.58-5.01	1.66	0.64-4.31	10678	14	1.10	0.51-2.32	1.16	0.57-2.34	10492	200	1.07	0.89-1.29	1.04	0.86-1.26	10473	219	1.08	0.90-1.29	1.06	0.88-1.26
8d-3mo																								
No	18738	38					18704	72					18510	266					18081	695				
Yes	7911	18	1.12	0.60-2.01	1.16	0.65-2.08	7905	24	0.79	0.47-1.27	0.81	0.50-1.29	7778	151	1.35	1.09-1.66	1.37	1.11-1.68	7652	277	0.94	0.82-1.09	1.19	1.00-1.42
3m-6mo																								
No	22135	102					22030	207					22130	107					21399	838				
Yes	4446	22	1.07	0.64-1.72	1.09	0.68-1.76	4432	36	0.86	0.59-1.24	0.94	0.65-1.35	4445	23	1.07	0.65-1.69	1.10	0.69-1.75	4334	134	0.79	0.65-0.95	1.01	0.82-1.24

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

When similar analyses were done for any nasal bleeding, bruising or umbilical bleeding the adjusted odds ratio was 1.37 (95% CI 1.11-1.68) at 8 days to 3 months of age, indicating a 37% higher risk of this combination of bleeding significantly associated with exclusive breastfeeding.

When similar analysis was done for the risk of any bleeding for exclusive breastfeeding, for 3 months to 6 months of age, the crude odds of any bleeding for exclusively breast feeding was 0.79 (95% CI 0.65-0.95), reflecting 21% reduction of risk of any bleeding associated with exclusively breast feeding. When the odds ratio was adjusted, the protective effect of EBF disappeared and the association became non-significant (adjusted OR=1.01, 95% CI 0.82-1.24).

8.6 Association between Exclusive Breastfeeding and Bleeding Status among Cohort of Deceased Infants

A similar analysis was carried out to estimate the risks of bleeding by EBF status among the cohort of infants who had died during the first six months of life, for whom information was obtained by parental interviews usually within one month of the death of the infants. The relationships between exclusive breast feeding and risk of individual and combined symptoms were examined separately among deceased infants. Crude and adjusted odd ratios with 95% CI were calculated as done with the survivors to assess the direction and strength of association at each sequential age period (Table 8.6). The odds ratios of exclusive breastfeeding were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, morbidities, maternal age, parity, obstructed delivery and religion.

The crude odds of nasal bleeding if EBF versus not EBF was 0.35 (95% CI 0.14-0.71) in the 1st day of life. But when adjusted the odds ratio, EBF appeared to be associated with non-significant 54% higher risk for nasal bleeding in the first day of life (adjusted OR=1.54, 95% CI 0.36-6.52). Between 2 days to 7 days of age, the adjusted odds ratio was 3.01 (95% 1.36-6.65), reflecting a consistent, significant increased risk of nasal bleeding with EBF at this age (Table 8.6).

A similar pattern was observed for bruising. In the 1st day of life the crude odds ratio if EBF was 0.40 (95% CI 0.14-0.93) but increased to 3.04 (95% CI 0.64-14.35) after adjustment.

For umbilical bleeding the adjusted odds ratios in the 1st day of life (adjusted OR=0.89, 95% CI 0.37-2.17), for 8 days to 3 months of age (adjusted OR=0.73, 95% CI 0.39-1.363) and for 3 months to 6 months of age (adjusted OR=0.61, 95% CI 0.21-1.79), but the 95% CI were not statistically significant. For fresh intestinal bleeding the direction of the adjusted odds ratio was protective for EBF for the age interval 8 days to 3 months (adjusted OR=0.15, 95% CI 0.02-1.22), although statistically non-significant.

Table 8.6: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to EBF among deceased infants

Exclusive Breastfeeding	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
1st day (<24 hr)																								
No	2411	74	1				2429	56					2401	84					2485	0				
Yes	647	7	0.35	0.14-0.71	1.54	0.36-6.52	648	6	0.40	0.14-0.93	3.04	0.64-14.35	636	18	0.81	0.45-1.37	0.89	0.37-2.17	652	2				
2-7 days																								
No	2520	59					2566	13					2508	71					2569	10				
Yes	537	23	1.83	1.07-3.04	3.01	1.36-6.65	557	3	1.07	0.19-3.89	1.16	0.31-4.39	537	23	1.51	0.89-2.47	0.73	0.39-1.36	560	0				
8d-3mo																								
No	2625	28					2643	10					2626	27					2626	27				
Yes	477	9	1.77	0.73-3.88	1.06	0.48-2.33	483	3	1.64	0.29-6.40	0.43	0.05-3.51	482	4	0.81	0.20-2.33	0.61	0.21-1.79	485	1	0.20	0.005-1.22	0.15	0.02-1.22
3m-6mo																								
No	2658	3					2659	2					2661	0					2654	1				
Yes	478	0					478	0					478	0					477	1	0.79	0.02-6.21	1.10	0.11-10.99

Exclusive Breastfeeding	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding/ Bruising / Umbilical Bleeding						Any Bleeding					
	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI
	No	Yes					No	Yes					No	Yes					No	Yes				
1st day(<24hr)																								
No	2361	124					2387	98					2287	198					2267	218	1			
Yes	642	12	0.36	0.18-0.65	2.02	0.69-5.86	639	15	0.57	0.31-0.99	1.93	0.73-5.08	626	28	0.52	0.33-0.78	1.34	0.66-2.72	620	34	0.57	0.38-0.83	1.27	0.66-2.44
2-7 days																								
No	2509	70					2502	77					2447	132					2416	163				
Yes	534	26	1.75	1.06-2.80	2.76	1.36-5.59	533	27	1.65	1.01-2.61	2.26	1.18-4.33	512	48	1.74	1.20-2.47	1.33	0.83-2.14	503	57	1.68	1.20-2.32	1.44	0.95-2.18
8d-3mo																								
No	2616	37					2603	50					2591	62					2535	118				
Yes	474	12	1.79	0.84-3.54	0.92	0.44-1.90	473	13	1.43	0.71-2.69	0.92	0.48-1.75	472	14	1.24	0.64-2.26	0.73	0.38-1.39	465	21	0.97	0.57-1.67	0.59	0.36-1.01
3m-6mo																								
No	2657	4					2651	10					2657	4					2641	20				
Yes	478	0					478	0					478	0					477	1	0.28	0.007-1.74	0.29	0.04-2.29

*adjusted for gender, rurality at birth, number of siblings, clostrum feeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

When the analyses were done for the combination of bleeding symptoms for the cohort of deceased infants, exclusive breastfeeding found to be significantly associated 2.76 times higher risk of classical onset (2-7 days of age) of either nasal bleeding or bruising (adjusted OR= 2.76 (95C IC 1.36-5.59).

It was found that the adjusted odds of either nasal bleeding or bulging fontanel associated with if EBF to be 2.26 (95% 1.18-4.33) at 2 days to 7 days of life indicating a significantly increased risk of either nasal bleeding or bulging fontanel in the cohort of deceased infants associated with EBF during that period.

Combined risk of nasal bleeding, umbilical bleeding or bruising was increased by 74% (Crude OR=1.74, 95% 1.20-2.47) for EBF infants in the deceased cohort from 2 to 7 days of age. However, the association weakened after adjustment (OR=1.33, 95% CI 0.83-2.14). The risk of any bleeding related to EBF was high and significant (Crude OR=1.68, 95% CI 1.20-2.32) at 2 days to 7 days, but the association became non-significant after adjustment for other variables (Adjusted OR=1.44, 95% CI 0.95-2.18).

8.7 Association between Colostrum Feeding and Bleeding Status of Cohorts of Surviving and Deceased Infants

According to the literature, colostrum is rich in vitamin K[5, 59] and thus may be protective for vitamin K deficiency bleeding in early infancy. Crude and adjusted odds ratios with 95% CI were calculated for report of giving colostrum for individual and combined bleeding symptoms (Table 8.7). The odds ratios of colostrum were adjusted by logistic regression for gender, maturity at birth, number of siblings, EBF, morbidities, maternal age, maternal parity, obstructed delivery and religion.

Table 8.7: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to colostrum feeding among surviving infants

Colostrum Feeding	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI
1st day < 24 hr	No	Yes					No	Yes																
No	1309	0					1308	1					1303	6					1308	1	1			
Yes	25071	2					25058	15	0.78	0.12-32.98	0.85	0.11-6.59	24957	116	1.01	0.45-2.81	0.87	0.38-1.98	25065	8	0.42	0.06-18.54	0.41	0.05-3.39
2-7 days																								
No	1309	0					1309	0					1292	17	1				1306	3	1			
Yes	25064	9					25065	8					24627	446	1.38	0.85-2.39	1.17	0.71-1.91	25041	32	0.56	0.17-2.84	0.45	0.13-1.54
8d-3mo																								
No	1309	0					1309	0					1291	18					1304	5	1			
Yes	25054	19					25036	37					24727	346	1.00	0.62-1.72	0.82	0.51-1.33	24944	129	1.35	0.56-4.23	1.21	0.49-3.00
3m-6mo																								
No	1307	2					1305	4					1309	0					1275	34	1			
Yes	25013	60	1.57	0.41-13.25	1.47	0.35-6.04	25015	58	0.76	0.28-2.87	0.77	0.28-2.13	25067	6					24541	532	0.81	0.57-1.19	0.81	0.52-1.24

Colostrum Feeding	Nasal Bleeding / Bruising						Nasal Bleeding/Bulging fontanel						Nasal Bleeding/Bruising/ Umbilical Bleeding						Any Bleeding					
	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI
< 24 hr	No	Yes					No	Yes					No	Yes					No	Yes				
No	1308	1					1306	3					1302	7	1				1297	12	1			
Yes	25056	17	0.89	0.14-37.11	0.94	0.12-7.21	25033	40	0.69	0.22-3.52	0.72	0.22-2.37	24943	130	0.97	0.46-2.46	0.85	0.39-1.83	24908	165	0.72	0.39-1.42	0.65	0.36-1.18
2-7 days																								
No	1309	0					1308	1					1292	17	1				1291	18	1			
Yes	25056	17					25041	32	1.67	0.28-68.09	1.71	0.23-12.61	24616	457	1.41	0.87-2.45	1.19	0.73-1.96	24572	501	1.46	0.91-2.49	1.26	0.78-2.02
8d-3mo																								
No	1309	0					1306	3					1291	18	1				1280	29	1			
Yes	25017	56					24981	92	1.60	0.53-7.93	1.53	0.48-4.87	24676	397	1.15	0.72-1.97	0.95	0.59-1.53	24481	592	1.07	0.73-1.61	0.91	0.62-1.34
3m-6mo																								
No	1303	6					1297	12					1303	6	1				1251	58	1			
Yes	24955	118	1.03	0.46-2.86	0.99	0.44-2.29	24842	231	1.01	0.56-1.98	0.99	0.55-1.99	24949	124	1.08	0.48-3.06	1.06	0.46-2.41	24165	908	0.81	0.62-1.08	0.81	0.59-1.09

*adjusted for gender, maturity at birth, number of siblings, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

Table 8.8: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to colostrum feeding among deceased infants

Colostrum Feeding	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI
1st day (<24hr)	No	Yes					No	Yes					No	Yes					No	Yes				
No	153	2	1				154	1	1				151	4	1				156	0				
Yes	1567	16	0.78	0.18-7.07			1570	13	1.28	0.19-54.53			1538	45	1.10	0.39-4.29	0.92	0.21-4.10	1581	2				
2-7 days																								
No	152	3	1				154	1	1				150	5	1				155	0				
Yes	1539	44	1.45	0.46-7.38	0.89	0.20-3.96	1574	9	0.88	0.12-38.84			1511	72	1.43	0.57-4.60	1.42	0.50-4.02	1575	8				
8d-3mo																								
No	153	2	1				155	0					152	3	1				154	1	1			
Yes	1548	35	1.72	0.44-14.98	1.87	0.43-8.01	1570	13					1556	27	0.88	0.27-4.58	0.67	0.19-2.29	1560	23	2.27	0.36-94.11	1.89	0.22-[illegible]09
3m-6mo																								
No	155	0					155	0					155	0					155	0				
Yes	1580	3					1581	2					1583	0					1576	5				

Colostrum Feeding	Nasal Bleeding / Bruising						Nasal Bleeding/ Bulging Fontanel						Nasal Bleeding / Bruising /Umbilical Bleeding						Any bleeding					
	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI
1st day (<24hr)	No	Yes					No	Yes					No	Yes					No	Yes				
No	152	3	1				152	3	1				150	5	1				149	6	1			
Yes	1557	26	0.85	0.25-4.42	0.79	0.08-7.76	1553	30	0.98	0.29-5.07	1.47	0.17-12.39	1515	68	1.34	0.54-4.35	1.29	0.29-5.78	1504	79	1.30	0.56-3.72	1.65	0.38-7.24
2-7 days																								
No	151	4	1				149	6	1				149	9	1				142	13	1			
Yes	1531	52	1.28	0.46-4.95	1.25	0.29-5.38	1526	57	0.93	0.39-2.68	0.55	0.21-1.47	1465	118	1.31	0.65-2.99	1.24	0.53-2.95	1438	145	1.10	0.60-2.17	1.08	0.53-2.22
8d-3mo																								
No	153	2	1				149	6	1				150	5	1				145	10	1			
Yes	1536	47	2.34	0.60-20.08	2.42	0.57-10.25	1528	55	0.89	0.38-2.58	0.98	0.40-2.36	1513	70	1.38	0.55-4.47	1.25	0.48-3.21	1460	123	1.22	0.62-2.67	1.09	0.55-2.17
3m-6mo																								
No	155	0					155	0					155	0					155	0				
Yes	1579	4					1573	10					1579	4					1565	18				

*adjusted for gender, maturity at birth, number of siblings, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

In the surviving cohort, the adjusted odds of bruising if colostrum was fed to an infant in the 1st day of life was 0.85 (95% CI 0.11-6.59), for umbilical bleeding 0.87 (95% CI 0.38-1.98) and for fresh intestinal bleeding 0.41 (95% CI 0.05-3.39), reflecting reduction of risk of bleeding associated with colostrum feeding in the first day of life, although neither sets of associations were statistically significant (Table 8.7).

In the cohort of deceased infants, the adjusted odds of umbilical bleeding if colostrum fed was 0.92 (95% CI 0.21-4.10) in the first day of life, indicating 8% reduction in risk of bleeding non-significantly associated with colostrum feeding (Table 8.8). The adjusted odds ratio for nasal bleeding was 0.89 (95% CI 0.20-3.96) at 2 days to 7 days of age and the adjusted odds ratio for umbilical bleeding was 0.67 (95% CI 0.19-2.29) at 8 days to 3 months, indicating varying degrees of risk reduction, although neither of the associations were statistically significant.

8.8 Summary Findings of Chapter 8

Given the importance of breastfeeding in the literature as a potential causal determinant of bleeding related to vitamin K deficiency in early life, the infantile bleeding status was analyzed by patterns of breastfeeding in both cohorts of surviving and deceased infants separately in this chapter. The direction and strength of association between exclusive breastfeeding and risk of individual bleeding and combination of bleeding symptoms were also analyzed based on age of onset for both surviving and deceased infants separately. Similar analysis with colostrum feeding was also done. About 95% of surviving and 90.6% of deceased infants were fed colostrum. Almost all of the infants (99.3%) surviving to 6 months of age and about 93% of deceased infants before death were breastfed. Among the surviving infants, 42.7% were exclusively breastfed in the first day of life, 40% at 2 days to 7 days of age, 29.7% at 8 days to 3 months of age and 16.7% at 3 months to 6months of age (Table 8.2). In the deceased cohort, 20.8% of infants had been exclusively breastfed in the first day of life, 17.8% at 2 days to 7 days of age, 15.5% at 8 days to 3 months of age and 15.2% at 3 months to 6 months of age (Table 8.4). A significantly higher percentage of infants who had bleeding (25.9%) had been exclusively breastfed compared to infants who did not have bleeding (17.2%) at 2 day 7 days age ($p=<0.001$) prior to deaths in the deceased cohort.

Exclusive breastfeeding appeared to be significantly associated with increased risk of bleeding at 8 days to 6 months of age for the cohort of surviving infants and up to 7 days of life for the cohort of deceased infants. On the other hand, analysis with colostrum feeding revealed that colostrum feeding was non-significantly associated with lower risk of bleeding in the first day of life for cohort of surviving infants and up to 3 months of life for the cohort of deceased infants.

Chapter 9: Analysis of Some Other Determinants

From the literature review it is found that gender[3,5,8,11,21], maturity at birth[23,42], obstructed labor[23], colostrum feeding[5,71], exclusive breastfeeding[3-5,10,23,42], morbidities of infants[10,11,21,23,] and maternal drug intake (anticonvulsants and anti-tubercular) during pregnancy[10,21,23] are associated with vitamin K deficiency bleeding of infants. The preceding section (Chapter 8) dealt with exclusive breastfeeding and colostrum feeding. In this section, analyses of a few more variables that might be associated with risks of bleeding disorders in early infancy have been analyzed.

In this chapter, associations between bleeding status and gender, maturity at birth, number of siblings, obstructed labor, infants' morbidities (e.g. cough, high fever, breathing difficulties, diarrhoea, dysentery), maternal parity and religion have been reported. The risk of individual bleeding e.g. nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding (red blood stool) and combined symptoms of bleeding were analyzed at each sequential age as <24hours (1st day), 2days to 7 days, 8 days to 3 months and 3 months to 6 months as in previous analyses among surviving and deceased infants. Estimates of risks were adjusted for potential confounders.

9.1 Association between Gender and Bleeding Status among Cohort of Surviving and Deceased Infants

The relationship between gender and risk of individual and combined bleeding symptoms were examined separately in both the cohort of surviving and deceased infants as a means of assessing the consistency in association and controlling for potential confounders.

Table 9.1A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to gender among surviving infants

	Nasal bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
			Crude		Adjusted				Crude		Adjusted				Crude		Adjusted				Crude		Adjusted	
	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI	Bleeding status		OR	95%CI	OR	95%CI
	No	Yes					No	Yes					No	Yes					No	Yes				
Gender																								
1st day																								
Female	13202	2					13197	7	1				13146	58	1				13198	6	1			
Male	15501	0					13492	9	1.26	0.42-3.97	1.04	0.38-2.89	13437	64	1.08	0.74-1.57	1.03	0.72-1.48	13498	3	0.49	0.08-2.29	0.41	0.10-1.63
2-7 days																								
Female	13198	6	1				13199	5	1				12971	233	1				13189	15	1			
Male	13498	3	0.49	0.79-2.29	0.45	0.11-1.81	13498	3	0.59	0.09-3.02	0.55	0.13-2.32	13266	235	0.99	0.82-1.19	0.97	0.80-1.17	13481	20	1.30	0.63-2.74	0.99	0.50-1.98
8 days-3mo																								
Female	13196	8	1				13189	15	1				13013	191	1				13156	48	1			
Male	13490	11	1.35	0.49-3.85	1.49	0.58-3.89	13479	22	1.44	0.71-2.98	1.40	0.71-2.77	13326	175	0.89	0.72-1.11	0.86	0.69-1.07	13414	87	1.78	1.23-2.59	1.48	1.03-2.12
3-6 mo																								
Female	13176	28	1				13168	36	1				13202	2	1				12970	234	1			
Male	13467	34	1.19	0.70-2.03	1.15	0.69-1.90	13475	26	0.71	0.41-1.20	0.66	0.39-1.12	13497	4	1.96	0.28-21.62	2.04	0.37-11.25	13165	336	1.41	1.19-1.68	1.02	0.83-1.24
Gender	Nasal bleeding / Bruising						Nasal bleeding / Bulging Fontanel						Nasal bleeding /Bruising / Umbilical Bleeding						Any Bleeding					
1st day																								
Female	13195	9	1				13181	23	1				13138	66	1				13118	86	1			
Male	13492	9	0.98	0.34-2.78	0.84	0.32-2.19	13481	20	0.85	0.44-1.62	0.84	0.46-1.53	13430	71	1.05	0.74-1.50	0.99	0.71-1.40	13410	91	1.04	0.76-1.41	0.99	0.74-1.34
2-7 days																								
Female	13193	11	1				13185	19	1				12963	241	1				12940	264	1			
Male	13495	6	0.53	0.16-1.57	0.51	0.19-1.38	13487	14	0.72	0.33-1.52	0.64	0.32-1.31	13263	238	0.97	0.80-1.16	0.94	0.78-1.13	13241	260	0.96	0.81-1.15	0.94	0.79-1.12
8 days-3mo																								
Female	13181	23	1				13154	50	1				12992	212	1				12905	299	1			
Male	13468	33	1.40	0.80-2.51	1.44	0.83-2.51	13455	46	0.90	0.60-1.37	0.83	0.55-1.26	13296	205	0.95	0.78-1.52	0.91	0.75-1.11	13175	326	1.07	0.91-1.26	1.00	0.85-1.18
3-6 mo																								
Female	13140	64	1				13089	115	1				13138	66	1				12773	431	1			
Male	13441	60	0.92	0.63-1.36	0.87	0.61-1.25	13373	128	1.09	0.84-1.42	1.03	0.79-1.33	13437	64	0.95	0.66-1.36	0.92	0.65-1.31	12960	541	1.24	1.09-1.41	1.00	0.87-1.15

*adjusted for maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

Table 9.1B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to gender among deceased infants

	Nasal bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Gender																								
1st day																								
Female	1383	35	1				1388	30	1				1376	42	1				1417	1	1			
Male	1675	46	1.09	0.68-1.75	0.25	0.05-1.26	1689	32	0.88	0.51-1.50	1.32	0.28-6.18	1661	60	1.18	0.78-1.81	0.92	0.40-2.09	1720	1	0.82	0.01-64.71	0.98	0.06-15.69
2-7 days																								
Female	1378	40	1				1408	10	1				1378	40	1				1413	5	1			
Male	1679	42	0.86	0.54-1.37	1.38	0.61-3.09	1715	6	0.49	0.15-1.50	0.68	0.21-2.17	1667	54	1.12	0.72-1.72	1.16	0.69-1.95	1716	5	0.82	0.19-3.59	0.48	0.09-2.70
8 days-3mo																								
Female	1406	12	1				1408	10	1				1402	16	1				1403	15	1			
Male	1696	25	1.73	0.83-3.79	1.77	0.87-3.63	1718	3	0.25	0.04-0.96	0.42	0.11-1.64	1706	15	0.77	0.35-1.67	0.89	0.41-1.93	1708	13	0.71	0.31-1.61	0.83	0.33-2.07
3-6 mo																								
Female	1416	2	1				1417	1	1				1418	0					1411	7	1			
Male	1720	1	0.41	0.007-7.92	0.38	0.03-4.36	1720	1	0.82	0.01-64.7	0.82	0.05-13.11	1721	0					1720	1	0.12	0.002-0.91	0.06	0.01-0.69
Gender	**Nasal bleeding / Bruising**						**Nasal bleeding /Bulging Fontanel**						**Nasal bleeding / Bruising / Umbilical Bleeding**						**Any Bleeding**					
1st day																								
Female	1357	61	1				1369	49	1				1322	96	1				1310	108	1			
Male	1646	75	1.01	0.71-1.46	1.27	0.29-5.46	1657	64	1.08	0.73-1.61	1.43	0.44-4.58	1591	130	1.13	0.85-1.50	0.90	0.43-1.91	1577	144	1.11	0.85-1.45	1.07	0.54-2.13
2-7 days																								
Female	1370	48	1				1369	49	1				1334	84	1				1318	100	1			
Male	1673	48	0.82	0.53-1.26	1.02	0.51-2.07	1666	55	0.92	0.61-1.39	1.06	0.56-2.01	1625	96	0.94	0.69-1.28	1.16	0.74-1.82	1601	120	0.99	0.74-1.31	1.05	0.71-1.55
8 days-3mo																								
Female	1397	21	1				1391	27	1				1382	36	1				1348	70	1			
Male	1693	28	1.10	0.60-2.05	1.33	0.72-2.47	1685	36	1.10	0.65-1.89	1.33	0.77-2.28	1681	40	0.91	0.56-1.48	1.08	0.65-1.79	1652	69	0.80	0.56-1.15	1.03	0.71-1.51
3-6 mo																								
Female	1415	3	1				1411	7	1				1415	3	1				1402	16	1			
Male	1720	1	0.27	0.005-3.4	0.28	0.03-2.69	1718	3	0.35	0.06-1.55	0.34	0.09-1.35	1720	1	0.27	0.005-3.42	0.28	0.03-2.69	1716	5	0.25	0.07-0.73	0.23	0.08-0.66

*adjusted for maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion.

The crude and adjusted odd ratios with 95% CI were calculated to assess the association between gender and onset of bleeding at each sequential age for both surviving (Table 9.1 A) and deceased infants (Table 9.1 B) separately. For assessing the independent effect of gender on bleeding symptoms the odds ratios of gender were adjusted by logistic regressions for maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion.

The crude odds of fresh intestinal bleeding (red blood in stool) associated with male babies relative to the odds of fresh intestinal bleeding for female babies was 1.78 (95% CI 1.23-2.59) at 8 days to 3 months of age, reflecting 78% higher risk of fresh intestinal bleeding significantly associated with male babies among surviving infants. When the odds ratio were adjusted, the adjusted odds of fresh intestinal bleeding for male babies was 1.48 (95% CI 1.03-2.12) at 8 days to 3 months of age, reflecting 48% higher risk of fresh intestinal bleeding significantly associated with if babies were male among surviving infants (Table 9.1A).

Similar analysis for deceased infants was done. The crude odds of bruising associated with male babies relative to female babies was 0.25 (95% CI 0.04-0.96) at 8 days to 3 months of age, reflecting 75% lower risk of bruising associated with male gender. When the odds ratio was adjusted, the odds ratio became statistically non-significant (adjusted OR=0.42, 95% CI 0.11-1.64), reflecting non significant association of bruising with gender of babies among deceased infants (Table 9.1B).

When analyses were done for combination of bleeding symptoms, although the direction and magnitude of the adjusted odds ratios were towards increased risk associated with male gender up to 3 months of age, but neither sets of the adjusted odds ratios were statistically significant.

9.2 Association between Maturity at Birth and Bleeding Status among Cohorts of Surviving and Deceased Infants

The relationship between maturity at birth and risk of individual and combined bleeding symptoms were examined separately among cohorts of both surviving and deceased infants as a means of assessing the consistency in association and controlling for potential confounders. The crude and adjusted odd ratios with 95% CI were calculated to assess the association between maturity at birth and onset of bleeding at each sequential age for both surviving (Table 9.2A) and deceased infants (Table 9.2B) separately. Prematurity was defined as gestational age at < 37 weeks and maturity as gestational age at >=37 weeks. For assessing the independent effect of maturity at birth on bleeding symptoms the odds ratios of maturity at birth were adjusted by logistic regressions for gender, number of siblings, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, parity, obstructed delivery and religion. The crude odds of bruising if premature babies versus mature babies was 3.29 (95% CI 1.08-10.07) in the first day of life, reflecting 3.29 times higher risk of bruising associated with premature babies among surviving infants. When the odds ratio was adjusted, the adjusted odds of bruising associated premature relative to the mature babies was 4.15 (95% CI 1.49-11.53) in the first day of life, reflecting 4.15 times increased risk bruising significantly associated with prematurity among surviving infants (Table 9.2A).

Table 9.2A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to maturity at birth among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Frank Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Maturity																								
1st day																								
Mature	20415	1	1				20408	8	1				20316	100	1				20407	9				
Premature	6205	1	3.29	0.42-258.26	1.48	0.07-29.38	6198	8	3.29	1.08-10.07	4.15	1.49-11.53	6184	22	0.72	0.43-1.16	0.74	0.47-1.18	6206	0				
2-7 days																								
Mature	20409	7	1				20411	5	1				20054	362	1				20389	27	1			
Premature	6204	2	0.94	0.09-4.94	0.98	0.20-4.75	6203	3	1.97	0.31-10.15	2.00	0.48-8.42	6103	103	0.93	0.74-1.17	0.93	0.74-1.16	6198	8	0.97	0.38-2.21	0.82	0.36-1.84
8-3 mo																								
Mature	20401	15	1				20390	26	1				20135	281	1				20324	92	1			
Premature	6202	4	0.88	0.21-2.75	0.67	0.19-2.32	6195	11	1.39	0.62-2.92	1.44	0.70-2.95	6122	84	0.98	0.76-1.26	1.00	0.78-1.29	6163	43	1.54	1.05-2.24	1.34	0.92-1.96
3-6 mo																								
Mature	20364	52	1				20364	52	1				20411	5	1				20000	416	1			
Premature	6196	10	0.63	0.29-1.26	0.65	0.33-1.27	6197	9	0.57	0.25-1.17	0.59	0.29-1.20	6205	1	0.66	0.01-5.88	0.67	0.08-5.76	6055	151	1.19	0.99-1.45	1.08	0.86-1.35

	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical Bleeding						Any Bleeding					
Maturity																								
1st day																								
Mature	20407	9	1				20385	31	1				20309	107	1				20280	136	1			
Premature	6197	9	3.29	1.16-9.37	3.84	1.46-10.14	6194	12	1.27	0.59-2.55	1.30	0.66-2.56	6176	30	0.92	0.59-1.39	0.97	0.64-1.45	6165	41	0.99	0.68-1.42	1.03	0.72-1.46
2-7 days																								
Mature	20404	12	1				20393	23	1				20046	370	1				20013	403	1			
Premature	6201	5	1.37	0.38-4.18	1.39	0.49-3.97	6196	10	1.43	0.61-3.13	1.46	0.68-3.13	6100	106	0.94	0.75-1.17	0.94	0.75-1.17	6088	118	0.96	0.78-1.87	0.95	0.77-1.18
8-3 mo																								
Mature	20375	41	1				20342	74	1				20097	319	1				19945	471	1			
Premature	6191	15	1.20	0.62-2.22	1.14	0.61-2.09	6184	22	0.98	0.58-1.59	0.91	0.55-1.49	6109	97	1.00	0.79-1.26	1.0	0.79-1.27	6053	153	1.07	0.89-1.29	1.04	0.86-1.25
3-6 mo																								
Mature	20312	104	1				20220	196	1				20307	109					19679	737	1			
Premature	6187	19	0.59	0.35-0.98	0.62	0.38-1.02	6160	46	0.77	0.55-1.07	0.73	0.53-1.02	6186	20	0.60	0.35-0.98	0.64	0.40-1.03	5978	228	1.02	0.87-1.19	0.94	0.79-1.11

*adjusted for gender, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

Table 9.2B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to maturity at birth among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Maturity																								
1st day																								
Mature	1220	26	1				1234	12	1				1217	29	1				1246	0				
Premature	1735	54	1.46	0.89-2.44	1.63	0.37-7.25	1741	48	2.84	1.48-5.89	1.29	0.28-5.98	1721	68	1.66	1.05-2.67	2.04	0.87-4.79	1787	2				
2-7 days																								
Mature	1227	19	1				1239	7	1				1212	34	1				1242	4	1			
Premature	1728	61	2.28	1.33-4.06	1.38	0.60-3.15	1780	9	0.89	0.29-2.84	1.31	0.39-4.31	1729	60	1.24	0.79-1.96	1.94	1.12-3.36	1783	6	1.04	0.25-5.04	1.32	0.24-7.32
8-3 mo																								
Mature	1228	18	1				1237	9	1				1228	18	1				1230	16	1			
Premature	1771	18	0.69	0.34-1.42	0.96	0.48-1.93	1785	4	0.31	0.07-1.10	0.34	0.08-1.40	1776	13	0.50	0.22-1.08	0.71	0.32-1.56	1777	12	0.52	0.22-1.17	0.69	0.28-1.69
3-6 mo																								
Mature	1245	1	1				1244	2					1246	0					1241	5	1			
Premature	1787	2	1.39	0.07-82.26	2.23	0.19-26.23	1789	0					1789	0					1786	3	0.42	0.06-2.15	0.59	0.12-3.00
Maturity	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical bleeding**						**Any Bleeding**					
1st day																								
Mature	1208	38	1				1210	36	1				1182	64	1				1173	73	1			
Premature	1694	95	1.78	1.20-2.69	3.43	0.67-17.83	1714	75	1.47	0.97-2.27	5.84	1.26-26.94	1635	154	1.74	1.28-2.39	2.41	1.09-5.30	1619	170	1.69	1.26-2.27	2.19	1.07-4.54
2-7 days																								
Mature	1221	25	1				1217	29	1				1189	57	1				1172	74	1			
Premature	1720	69	1.96	1.22-3.25	1.27	0.61-2.62	1716	73	1.79	1.14-2.87	1.59	0.82-3.10	1668	121	1.51	1.08-2.13	1.52	0.96-2.40	1645	144	1.39	1.03-1.88	1.63	1.08-2.44
8-3 mo																								
Mature	1220	26	1				1210	36	1				1204	42	1				1163	83	1			
Premature	1767	22	0.58	0.31-1.08	0.80	0.43-1.49	1764	25	0.48	0.27-0.82	0.65	0.38-1.13	1756	33	0.54	0.33-0.88	0.74	0.44-1.24	1735	54	0.44	0.30-0.63	0.59	0.39-0.86
3-6 mo																								
Mature	1244	2	1				1240	6	1				1244	2	1				1233	13				
Premature	1787	2	0.69	0.05-9.61	3.16	0.15-8.64	1785	4	0.46	0.09-1.96	0.73	0.20-2.67	1787	2	0.69	0.05-9.61	3.16	0.15-8.64	1781	8	0.43	0.15-1.11	0.68	0.26-1.74

*adjusted for gender, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

When analysis was conducted for combination of bleeding symptoms, the crude odds of nasal bleeding or bruising for premature babies relative to mature babies was 3.29 (95% CI 1.16-9.37) in the first day of life, reflecting 3.29 times increased risk of nasal bleeding or bruising associated with prematurity in the first day of life. The adjusted odds of either nasal bleeding or bruising for premature babies relative to mature was 3.84 (95% CI 1.46-10.14) in the first day of life, reflecting 3.84 times increased risk of either nasal bleeding or bruising significantly associated with prematurity in the first day of life among surviving infants (Table 9.2A).

Similar analysis was done for the cohort of deceased infants. The crude odds for bruising associated with prematurity at birth relative to maturity at birth was 2.84 (95% CI 1.48-5.89) in the 1st day of life, the crude odds for umbilical bleeding for prematurity at birth relative to mature at birth was 1.66 (95% CI 1.05-2.67) in the 1st day of life and the crude odds for nasal bleeding for prematurity at birth relative to the odds of nasal bleeding if mature at birth was 2.28 (95% CI 1.33-4.06) at 2 to 7 days of life, all reflecting direction of increased risks non-significantly associated with prematurity at birth for deceased infants (Table 9.2B). The crude odds of umbilical bleeding associated with premature at birth relative to the odds of umbilical bleeding if mature at birth was 1.24 (95%CI 0.79-1.96)) at 2 days to 7 days of age, reflecting 24% increased risk of umbilical bleeding non-significantly associated with prematurity. After adjustment, the odds ratio became statistically significant (adjusted OR=1.94, 95% CI 1.12-3.36), reflecting 94% increased risk of umbilical bleeding significantly associated with prematurity for deceased infants.

When analysis was done for combined bleeding symptoms, the adjusted odds of either nasal bleeding or bulging fontanel associated with premature at birth relative to mature at birth was 5.84 (95% CI 1.26-26.94) in the first day of life, reflecting 5.84 times increased risk of any nasal bleeding or bulging fontanel significantly associated with prematurity for deceased infants (Table 9.2B). The adjusted odds of either nasal bleeding, bruising or umbilical bleeding if premature at birth versus if mature at birth was 2.41 (95% CI 1.09-5.30) in the first day of life, reflecting 2.41 times increased risk of either nasal bleeding, bruising or umbilical bleeding significantly associated with prematurity. The adjusted odds of any bleeding associated with prematurity at birth relative to maturity at birth was 2.19 (95% CI 1.07-4.54) in the first day of life, reflecting 2.19 times increased risk of any bleeding significantly associated with prematurity. Similar analysis with any bleeding for 2 to 7 days of age showed, prematurity was significantly associated with 63% higher risk of any bleeding (adjusted OR =1.63, 95% CI 1.08-2.44) among deceased infants (Table 9.2B).

9.3 Association between Numbers of Siblings and Bleeding Status among Cohorts of Surviving and Deceased Infants

The relationship between number of siblings and risk of individual and combined bleeding symptoms were examined separately among cohorts of both surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. The crude and adjusted odd ratios with 95% CI were calculated to assess the association between number of siblings at birth and onset of bleeding at each sequential age for both surviving (Table 9.3A) and deceased infants (Table 9.3B) separately.

For assessing the independent effect of number of siblings on bleeding symptoms the odds ratios of number of siblings were adjusted by logistic regressions for gender, maturity at birth, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion. The crude odds of fresh intestinal bleeding associated with twins relative to singletons was 6.18 (95% CI 2.41-13.30) at 3 months to 6 months of age, reflecting 6.18 times increased risk of fresh intestinal bleeding significantly associated with twins. The adjusted odds of fresh intestinal bleeding for twins relative to singletons was 4.66 (95% CI 2.03-10.68) at 3 months to 6 months of age, reflecting 4.66 times increased risk of fresh intestinal bleeding significantly associated with twins among surviving infants (Table 9.3A).

When analysis for combination of bleeding symptoms was done, the crude odds for either nasal bleeding or bulging fontanel for twins relative to singletons was 2.53 (95% CI 0.34-19.02) in the 1st day of life, the crude odds ratios for similar bleeding for 2 to 7 days was 2.91 (95%CI 0.38-22.33), for 8days to 3 months the odds ratio was 1.06 (95% CI 0.14-7.79) and for 3 months to 6 months the odds ratio was 1.58 (95% CI 0.49-5.03), all reflecting a direction of increased risk of either nasal bleeding or bulging fontanel non-significantly associated with twins among surviving infants (Table 9.3A). The crude odds of any bleeding associated with twins relative to the odds of any bleeding if singleton was 2.42 (95% CI 1.26-4.25) at 3 months to 6 months of age, reflecting 2.19 times increased risk of any bleeding associated with twins babies.

Table 9.3A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to number of siblings at birth among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Siblings																								
1st day																								
Singleton	26464	1	1				26449	16					26343	122					26456	9				
Twins	239	1	110.7	1.40-8691.5	91.09	4.39-1891.74	240	0					240	0					240	0				
2-7 days																								
Singleton	26456	9					26457	8					25999	466	1				26431	34	1			
Twins	240	0					240	0					238	2	0.47	0.06-1.72	0.43	0.11-1.75	239	1	3.25	0.08-19.56	2.82	0.06-22.27
8d-3mo																								
Singleton	26446	19					26428	37					26105	360	1				26337	128	1			
Twins	240	0					240	0					234	6	1.85	0.67-4.15	1.75	0.76-4.02	233	7	6.18	2.41-13.30	4.66	2.03-10.68
3-6 mo																								
Singleton	26403	62					26404	61	1				26459	6					25900	565	1			
Twins	240	0					239	1	1.81	0.05-10.57	2.35	0.32-17.45	240	0					235	5	0.98	0.31-2.32	0.62	0.23-1.67
Siblings	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical bleeding**						**Any Bleeding**					
1st day																								
Singleton	26448	17	1				26423	42	1				26329	136	1				26289	176	1			
Twins	239	1	6.51	0.16-41.87	4.83	0.61-38.34	239	1	2.63	0.06-15.63	2.53	0.34-19.02	239	1	0.81	0.02-4.63	0.77	0.11-5.60	239	1	0.62	0.02-3.56	0.59	0.08-4.33
2-7 days																								
Singleton	26448	17					26433	32	1				25988	477	1				25946	519	1			
Twins	240	0					239	1	3.46	0.08-20.87	2.91	0.38-22.33	238	2	0.46	0.05-1.68	0.21	0.03-1.51	235	5	1.06	0.34-2.53	0.98	0.40-2.41
8d-3mo																								
Singleton	26409	56					26370	95	1				26054	411	1				25853	612	1			
Twins	240	0					239	1	1.16	0.03-6.69	1.06	0.14-7.79	234	6	1.63	0.59-3.62	1.02	0.37-2.78	227	13	2.42	1.26-4.25	2.19	1.23-3.92
3-6 mo																								
Singleton	26342	123	1				26225	240	1				26336	129	1				25501	964	1			
Twins	239	1	0.89	0.02-5.13	1.11	0.15-8.05	237	3	1.38	0.28-4.14	1.58	0.49-5.03	239	1	0.85	0.02-4.89	2.08	0.51-8.63	232	8	0.91	0.39-1.83	0.72	0.33-1.57

*adjusted for gender, maturity at birth, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

Table 9.3B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to number of siblings at birth among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Siblings																								
1st day																								
Singleton	2713	65	1				2729	49	1				2690	88	1				2776	2				
Twins	345	16	1.94	1.03-3.43	4.41	0.88-21.97	348	13	2.08	1.02-3.94	2.31	0.23-22.82	347	14	1.23	0.64-2.21	0.35	0.04-2.76	361	0				
2-7 days																								
Singleton	2707	71	1				2764	14	1				2694	84	1				2769	9	1			
Twins	350	11	1.19	0.57-2.30	2.13	0.67-6.82	359	2	1.09	0.12-4.82	1.55	0.31-7.81	351	10	0.91	0.42-1.79	0.85	0.32-2.26	360	1	0.85	0.02-6.19	0.86	0.0[illegible]-9.70
8d-3mo																								
Singleton	2743	35	1				2766	12	1				2748	30	1				2752	26	1			
Twins	359	2	0.44	0.05-1.71	1.10	0.24-4.96	360	1	0.64	0.01-4.35	1.79	0.20-15.65	360	1	0.25	0.006-1.54	0.43	0.05-3.29	359	2	0.59	0.07-2.37	0.23	0.0[illegible]-2.18
3-6 mo																								
Singleton	2775	3					2776	2					2778	0					2770	8				
Twins	361	0					361	0					361	0					361	0				
Siblings	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical bleeding**						**Any Bleeding**					
1st day																								
Singleton	2669	109	1				2682	96	1				2590	188	1				2564	214	1			
Twins	334	27	1.97	1.23-3.09	3.92	0.56-27.56	344	17	1.38	0.76-2.36	2.78	0.51-15.13	323	38	1.62	1.09-2.36	0.61	0.13-2.76	323	38	1.41	0.95-2.04	0.59	0.13-2.62
2-7 days																								
Singleton	2695	83	1				2685	93	1				2620	158	1				2581	197	1			
Twins	348	13	1.21	0.61-2.22	1.49	0.48-4.62	350	11	0.91	0.43-1.72	1.36	0.45-4.10	339	22	1.08	0.65-1.72	0.62	0.24-1.62	338	23	0.89	0.54-1.40	1.05	0.52-2.15
8d-3mo																								
Singleton	2732	46	1				2717	61	1				2705	73	1				2645	133	1			
Twins	358	3	0.49	0.09-1.56	1.24	0.36-4.29	359	2	0.25	0.03-0.94	0.64	0.15-2.75	358	3	0.31	0.06-0.95	0.21	0.03-1.54	355	6	0.34	0.12-0.76	0.49	0.19-1.28
3-6 mo																								
Singleton	2774	4					2768	10					2774	4					2758	20	1			
Twins	361	0					361	0					361	0					360	1	0.38	0.009-2.41	0.41	3.34

*adjusted for gender, maturity at birth, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

The adjusted odds of any bleeding for twins versus if singleton was 2.19 (95% CI 1.23-3.92) at 3 months to 6 months of age, reflecting 2.19 times increased risk of any bleeding significantly associated with twins babies among surviving infants (Table 9.3A). Similar analysis was conducted for the cohort of deceased infants. The crude odds of nasal bleeding for twins relative to singletons was 1.94 (95% CI 1.03-3.43) in the 1st day of life, reflecting 94% increased of risk of nasal bleeding significantly associated with twins. When the odds ratio was adjusted, the association became non-significant (adjusted OR=4.41, 95% CI 0.88-21.97). Similarly, crude analysis showed twins to be significantly associated with bruising in the first day of life (crude OR=2.08, 95%CI 1.02-3.94) but when the odds ratio was adjusted, the association became non-significant (adjusted OR=2.31, 95% CI 0.23-22.82) for deceased infants (Table 9.3B). The crude odds of either nasal bleeding or bruising associated with twins relative to if singleton was 1.97 (95% CI 1.23-3.09) in the 1st day of life, reflecting 97% increased risk of any nasal bleeding or bruising significantly associated with twins. When the odds ratio was adjusted, the association became non-significant (adjusted OR=3.92, 95% CI 0.56-27.56). Similarly, crude analysis showed twins to be significantly associated with either nasal bleeding, bruising or umbilical bleeding in the first day of life (crude OR=1.62, 95%CI 1.09-2.36) but when the odds ratio was adjusted, the association became non-significant (adjusted OR=0.61, 95% CI 0.13-2.76) for deceased infants (Table 9.3B)

9.4 Association between Birth Weights and Bleeding Status among Cohort of Surviving and Deceased Infants

The crude and adjusted odd ratios with 95% CI were calculated to assess the association between birth weights and onset of bleeding at each sequential age for both surviving (Table 9.4A) and deceased infants (Table 9.4B) separately. For assessing the independent effect of birth weights on bleeding symptoms, the odds ratios of birth weights were adjusted by logistic regressions for gender, maturity at birth, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion. As the infant trial started mid way of maternal trial, birth weights for all babies were not measured as the infants' trial had only that arrangement. Birth weights of ~14,000 infants were measured and for those babies who were measured within 48 hours of births were used for this analysis and low birth weight was considered as <2.5kg and normal birth weights as >=2.5 kg.

The adjusted odds of umbilical bleeding associated with low birth weights relative to the odds of umbilical bleeding if normal birth weights, was 0.72(95% CI 0.53-0.97) at 2 days to 7 days of age, reflecting an 18% risk reduction of umbilical bleeding significantly associated low birth weights (Table 9.4A). Similarly the adjusted odds of either nasal bleeding, bruising or umbilical bleeding for low birth weights relative to normal birth weights was 0.73(95% CI 0.54-0.99) at 2 days to 7 days of age, again reflecting a 17% risk reduction of such combination of bleeding significantly associated low birth weights (Table 9.4A).

Table 9.4A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to birth weights among surviving infants

	Nasal bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Birth Weight																								
1st day																								
Normal	4877	0					4874	3	1				4834	43	1				4873	4	1			
LBW	5766	0					5763	3	0.85	0.11-6.32	0.83	0.16-4.44	5737	29	0.57	0.34-0.93	0.64	0.39-1.05	5765	1	0.21	0.004-2.14	0.25	0.03-2.33
2-7 days																								
Normal	4876	1	1				4875	2	1				4770	107	1				4871	6	1			
LBW	5764	2	1.69	0.09-99.83	1.44	0.12-17.65	5765	1	0.42	0.007-8.12	0.30	0.03-3.69	5682	84	0.66	0.49-0.89	0.72	0.53-0.97	5760	6	0.85	0.23-3.16	0.76	0.2-2.53
8-3 mo																								
Normal	4875	2	1				4870	7					4821	56	1				4858	19	1			
LBW	5764	2	0.85	0.06-11.7	0.92	0.13-6.76	5766	0					5704	62	0.94	0.64-1.37	1.03	0.70-1.50	5743	23	1.02	0.53-1.99	0.81	0.4-1.59
3-6 mo																								
Normal	4867	10	1				4862	15	1				4877	0					4777	100	1			
LBW	5753	13	1.09	0.45-2.80	1.44	0.62-3.39	5754	12	0.68	0.29-1.55	0.60	0.27-1.35	5766	0					5644	122	1.03	0.78-1.36	1.04	0.78-1.44
Birth Weight	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical Bleeding**						**Any Bleeding**					
1st day																								
Normal	4874	3	1				4865	12	1				4832	45	1				4821	56	1			
LBW	5763	3	0.85	0.11-6.32	0.83	0.16-4.44	5749	17	1.19	0.54-2.75	1.06	0.49-2.30	5735	31	0.58	0.35-0.94	0.65	0.40-1.05	5720	46	0.69	0.46-1.04	0.71	0.47-1.07
2-7 days																								
Normal	4874	3	1				4872	5	1				4769	108					4761	116	1			
LBW	5763	3	0.85	0.11-6.32	0.65	0.12-3.49	5754	12	2.03	0.67-7.37	1.86	0.63-5.47	5679	87	0.67	0.50-0.91	0.73	0.54-0.99	5672	94	0.68	0.51-0.90	0.73	0.55-0.97
8-3 mo																								
Normal	4868	9	1				4858	19	1				4812	65					4779	98	1			
LBW	5764	2	0.19	0.02-0.91	0.27	0.06-1.33	5753	13	0.58	0.26-1.23	0.49	0.24-1.05	5702	64	0.83	0.58-1.19	0.96	0.66-1.39	5672	94	0.81	0.60-1.09	0.83	0.61-1.12
3-6 mo																								
Normal	4852	25					4842	35	1				4852	25					4719	158	1			
LBW	5741	25	0.85	0.47-1.54	0.91	0.51-1.62	5716	50	1.21	0.77-1.92	1.29	0.82-2.02	5741	25	0.85	0.47-1.54	0.93	0.52-1.65	5571	195	1.05	0.84-1.30	1.07	0.83-1.37

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity, obstructed delivery and religion

Table 9.4B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to birth weights among deceased infants

	Nasal bleeding					Bruising					Umbilical Bleeding					*Fresh Intestinal Bleeding*				
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Birth Weight																								
1st day																								
Normal	79	0					79	0					72	7	1				79	0				
LBW	438	7					440	5					424	21	0.51	0.19-1.47	0.90	0.18-4.52	444	1				
2-7 days																								
Normal	78	1	1				79	0					76	3	1				79	0				
LBW	424	21	3.86	0.60-161.75	1.07	0.11-10.4	444	1					423	22	1.32	0.38-7.04	1.31	0.26-6.56	445	0				
8-3 mo																								
Normal	77	2	1				79	0					79	0					79	0				
LBW	435	10	0.89	0.18-8.46	0.39	0.05-2.92	444	1					436	9					438	7				
3-6 mo																								
Normal	79	0					79	0					79	0					78	1				
LBW	444	1					444	1					445	0					445	0				
Birth Weight	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical bleeding**						**Any Bleeding**					
1st day																								
Normal	79	0					78	1	1				72	7	1				72	7	1			
LBW	435	10					435	10	1.79	0.25-78.79	0.24	0.01-5.54	416	29	0.72	0.29-2.01	0.89	0.19-4.22	413	32	0.79	0.33-2.22	0.89	0.19-4.22
2-7 days																								
Normal	78	1					78	1	1				75	4	1				75	4	1			
LBW	423	22	4.06	0.64-169.5	1.43	0.16-12.97	421	24	4.45	0.70-185.13	1.39	0.15-13.04	405	40	1.85	0.64-7.33	1.06	0.27-4.12	400	45	2.11	0.74-8.30	1.25	0.32-4.79
8-3 mo																								
Normal	77	2					77	2	1				77	2	1				75	4	1			
LBW	434	11	0.98	0.21-9.23	0.52	0.08-3.47	431	14	1.25	0.28-11.55	1.28	0.23-7.18	426	19	1.72	0.40-15.48	1.64	0.33-88.10	416	29	1.31	0.44-5.26	1.68	0.49-5.69
3-6 mo																								
Normal	79	0					79	0					79	0					78	1				
LBW	444	1					443	2					444	1					442	3	0.53	0.04-28.14	0.92	0.05-15.93

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age maternal parity, obstructed delivery and religion

Similar analysis was done for the cohort of deceased infants. The crude odds of any bleeding for low birth weights versus if normal birth weights was 1.25(95% CI 0.33-4.79) at 2 days to 7 days of age and 1.68 (95% CI 0.49-5.69) at 8 days to 3 month of age, reflecting 25-68% increased risk associated with low birth weights for deceased infants, but the neither of the 95% CI were statistically significant. (Table 9.4B).

9.5 Association between Maternal Parity and Bleeding Status among Cohort of Surviving and Deceased Infants

The relationship between maternal parity and risk of individual and combined bleeding symptoms were examined separately among both cohorts of the surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between maternal parity and onset of bleeding at each sequential age for both cohorts of surviving (Table 9.5A) and deceased (Table 9.5B) infants separately. For assessing the independent effect of maternal parity on bleeding symptoms, the odds ratios of maternal parity were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, obstructed delivery and religion.

The crude odds of umbilical bleeding among babies if their mothers were multipara relative to among babies if mothers were nullipara was 1.98 (95% CI 1.29-3.12) in the first day of life, reflecting 98% higher risk of umbilical bleeding among babies significantly associated with maternal multiparity.

The adjusted odds of umbilical bleeding among babies if mothers were multipara versus if mothers were nullipara was 2.32 (95% CI 1.40-3.82) in the first day of life, reflecting 2.32 times higher risk of umbilical bleeding among babies significantly associated with maternal multiparity for surviving infants (Table 9.5A). Similar adjusted analysis with umbilical bleeding for 2 days to 7 days of age showed, maternal multiparity was significantly associated with 84% higher risk of umbilical bleeding (adjusted OR= 1.84, 95% CI 1.42-2.38). The pattern was similar for 8 days to 3 months of age, maternal multiparity was significantly associated with 85% higher risk of umbilical bleeding (adjusted OR =1.85, 95% CI 1.38-2.49).

When analysis was done for the combination of bleeding symptoms, the adjusted odds of either nasal bleeding, bruising or umbilical bleeding among babies if mothers were multipara versus among babies if mothers were nullipara was 2.14 (95% CI 1.40-3.82) in the first day of life, reflecting 2.14 times higher risk of such combination of bleeding among babies significantly associated with maternal multiparity. Similar adjusted analysis with nasal bleeding, bruising or umbilical bleeding for 2 to 7 days age showed, maternal multiparity was significantly associated with 89% higher risk of any nasal bleeding or bruising or umbilical bleeding (adjusted OR =1.89, 95% CI 1.46-2.45). Similar adjusted analysis with either nasal bleeding, bruising or umbilical bleeding for 8 days to 3 months of age showed, maternal multiparity was significantly associated with 63% higher risk of any nasal bleeding or bruising or umbilical bleeding (adjusted OR= 1.63, 95% CI 1.24-2.15).

The adjusted odds of any bleeding among babies associated with if mothers were multipara relative to babies if mothers were nullipara was 1.55 (95% CI 1.03-2.31) in the first day of life, reflecting 55% higher risk of any bleeding among babies significantly associated with maternal multiparity. Similar adjusted analysis with any bleeding for 2days to 7 days age showed, maternal multiparity was significantly associated with 76% higher risk of any bleeding (adjusted OR= 1.76, 95% CI 1.38-2.24). The pattern was similar for 8 days to 3 months of age, maternal multiparity was significantly associated with 30% higher risk of any bleeding (adjusted OR= 1.64, 95%CI 1.04-1.63) for surviving infants (Table 9.5A).

Similar analysis for the cohort of deceased infants was conducted. The adjusted odds of umbilical bleeding among babies associated with if mothers were multipara relative to babies if mothers were nullipara was 3.23 (95% CI 1.07-9.73) in the first day of life, reflecting 3.23 times higher risk of umbilical bleeding significantly associated with maternal multiparity for deceased infants (Table 9.5B).

When analysis for combination of bleeding symptoms was done, the crude odds of either nasal bleeding or bruising among babies if mothers were multipara versus babies if mothers were nullipara was 1.67 (95% CI 1.08-2.61) in the first day of life, reflecting 67% higher risk of either nasal bleeding, bruising significantly associated with maternal multiparity for deceased infants, but when the odds ratio was adjusted the association became statistically non-significant (adjusted OR=0.92, 95%CI 0.36-2.35).

Table 9.5A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to maternal parity among surviving infants

Parity	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
1st day																								
Nullipara	10169	0					10161	8	1				10140	29	1				10166	3	1			
Multipara	16498	2					16492	8	0.62	0.20-1.88	0.88	0.23-3.31	16407	93	1.98	1.29-3.12	2.32	1.40-3.82	16494	6	1.23	0.26-7.62	1.45	0.26-8.19
2-7 days																								
Nullipara	10167	2	1				10167	2	1				10058	111	1				10159	10	1			
Multipara	16493	7	2.16	0.41-21.29	4.61	0.74-28.84	16494	6	1.85	0.38-18.74	1.99	0.29-13.80	16145	355	1.59	1.60 2.49	1.84	1.42-2.38	16475	25	1.54	0.71-3.59	0.88	0.28-2.8
8 days-3mo																								
Nullipara	10162	7	1				10158	11	1				10082	87	1				10134	35	1			
Multipara	16489	11	0.97	0.34-2.95	0.99	0.29-3.54	16475	25	1.40	0.66-3.16	0.83	0.31-2.03	16221	279	1.99	1.56-2.57	1.85	1.38-2.49	16400	100	1.77	1.19-2.68	1.29	0.79-2.0
3-6 mo																								
Nullipara	10147	22	1				10142	27	1				10166	3	1				9963	206	1			
Multipara	16460	40	1.12	0.65-1.98	1.28	0.66-2.49	16465	35	0.80	0.47-1.37	0.99	0.51-1.91	16497	3	0.62	0.08-4.60	0.59	0.07-4.91	16137	363	1.09	0.91-1.29	0.86	0.66-1.1

Parity	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical bleeding						Any Bleeding					
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
1st day																								
Nullipara	10161	8	1				10151	18	1				10134	35	1				10115	54	1			
Multipara	16490	10	0.77	0.27-2.25	1.02	0.29-3.54	16475	25	0.86	0.45-1.67	0.86	0.39-1.90	16398	102	1.80	1.22-2.73	2.14	1.34-3.42	16377	123	1.41	1.01-1.98	1.55	1.03-2.31
2-7 days																								
Nullipara	10165	4	1				10157	12	1				10056	113	1				10041	128	1			
Multipara	16487	13	2.00	0.62-8.44	2.83	0.75-10.74	16479	21	1.08	0.51-2.41	1.17	0.47-2.90	16136	364	2.01	1.62-2.51	1.89	1.46-2.45	16106	394	1.92	1.57-2.36	1.76	1.38-2.24
8 days-3mo																								
Nullipara	10151	18	1				10132	37	1				10064	105	1				9993	176	1			
Multipara	16464	36	1.23	0.68-2.31	0.84	0.41-1.74	16442	58	0.97	0.63-1.50	0.79	0.46-1.35	16190	310	1.84	1.46-2.32	1.63	1.24-2.15	16053	447	1.58	1.32-1.89	1.30	1.04-1.63
3-6 mo																								
Nullipara	10120	49	1				10069	100	1				10017	52	1				9786	383	1			
Multipara	16425	75	0.94	0.65-1.38	1.12	0.70-1.77	16357	143	0.88	0.68-1.15	0.90	0.65-1.27	16422	78	0.92	0.64-1.34	1.04	0.66-1.64	15912	588	0.94	0.83-1.08	0.85	0.70-1.02

*adjusted for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, obstructed delivery and religion

Table 9.5B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to maternal parity among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Parity																								
1st day																								
Nullipara	1517	37	1				1518	36	1				1505	49	1				1554	0				
Multipara	1536	43	1.15	0.72-1.84	4.71	0.61-36.13	1553	26	0.71	0.41-1.21	0.44	0.05-3.67	1526	53	1.07	0.70-1.62	3.23	1.07-9.73	1577	2				
2-7 days																								
Nullipara	1521	33	1				1549	5	1				1502	42	1				1551	3	1			
Multipara	1530	49	1.48	0.92-2.38	0.65	0.22-1.91	1568	11	2.17	0.69-7.99	1.78	0.39-8.16	1527	52	1.23	0.79-1.89	1.28	0.65-2.52	1572	7	2.30	0.54-13.82	2.81	0.20-39.3
8 days-3mo																								
Nullipara	1531	23	1				1546	8	1				1542	12	1				1540	14	1			
Multipara	1565	14	0.59	0.28-1.21	1.40	0.55-3.54	1574	5	0.61	0.16-2.13	0.47	0.09-2.58	1560	19	1.57	0.72-3.55	1.17	0.43-3.22	1565	14	0.98	0.43-2.23	0.99	0.29-3.3
3-6 mo																								
Nullipara	1552	2	1				1554	0					1554	0					1550	4	1			
Multipara	1578	1	0.49	0.01-9.46	2.66	0.11-66.42	1577	2					1579	0					1575	4	0.98	0.18-5.29	1.18	0.12-11.8

	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical Bleeding						Any Bleeding					
Parity	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
1st day																								
Nullipara	1485	69	1				1494	60	1				1440	114	1				1418	136	1			
Multipara	1513	66	0.94	0.65-1.35	1.94	0.24-15.57	1528	51	0.83	0.57-1.24	0.49	0.09-2.61	1468	111	0.96	0.72-1.26	3.08	1.14-8.32	1465	114	0.81	0.62-1.06	1.66	0.67-4.09
2-7 days																								
Nullipara	1518	36	1				1509	45	1				1480	74	1				1455	99	1			
Multipara	1519	60	1.67	1.08-2.61	0.92	0.36-2.35	1520	59	1.30	0.86-1.98	0.63	0.27-1.49	1473	106	1.44	1.05-1.98	1.03	0.58-1.85	1458	121	1.22	0.92-1.62	0.73	0.43-1.22
8 days-3mo																								
Nullipara	1524	30	1				1515	39	1				1513	41	1				1484	70	1			
Multipara	1560	19	0.62	0.33-1.14	1.05	0.46-2.39	1555	24	0.60	0.34-1.03	0.93	0.45-1.90	1544	35	0.84	0.51-1.35	0.99	0.51-1.92	1510	69	0.97	0.68-1.38	0.85	0.52-1.39
3-6 mo																								
Nullipara	1552	2	1				1549	5	1				1552	2	1				1544	10	1			
Multipara	1577	2	0.98	0.07-13.59	4.06	0.31-53.71	1574	5	0.98	0.23-4.29	1.19	0.23-6.17	1577	2	0.98	0.07-13.59	4.06	0.31-53.71	1568	11	1.08	0.42-2.85	1.38	0.41-4.67

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, obstructed delivery and religion

The adjusted odds of either nasal bleeding, bruising or umbilical bleeding among babies associated if mothers were multipara relative to babies if mothers were nullipara was 3.08 (95% CI 1.14-8.32) in the first day of life, reflecting 3.08 times higher risk of umbilical bleeding significantly associated with maternal multiparity. The crude odds of either nasal bleeding, bruising or umbilical bleeding among babies if mothers were multipara versus babies if mothers were nullipara was 1.44 (95% CI 1.05-1.98) at 2 days to 7 days of age, reflecting 44% higher risk of either nasal bleeding, bruising or umbilical bleeding associated with maternal multiparity for deceased infants (Table 9.5B), but when the odds ratio was adjusted the association became statistically non-significant (crude OR=1.03, 95% CI 0.58-1.85).

9.6 Association between Obstructed Delivery and Bleeding Status among Cohorts of Surviving and Deceased Infants

The relationship between obstructed delivery and risk of individual and combined bleeding symptoms were also examined separately among cohorts of both surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Mothers were asked at the 3 months post-partum interviews whether they had obstructed labor for the index babies. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between obstructed delivery and onset of bleeding at each sequential age for both surviving (Table 9.6A) and deceased (Table 9.6B) infants separately.

For assessing the independent effect of obstructed delivery on bleeding symptoms the odds ratios of obstructed delivery were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity and religion.

When analysis for the cohort of surviving infants was done, the adjusted odds of umbilical bleeding if babies had obstructed delivery relative to if babies did not have obstructed delivery was 1.73 (95% CI 1.12-2.67) in the first day of life, reflecting 73% higher risk of umbilical bleeding significantly associated with obstructed delivery for surviving infants (Table 9.6A). Similar adjusted analysis with umbilical bleeding for 8 days to 3 months of age showed, obstructed delivery was significantly associated with 41% higher risk of umbilical bleeding (adjusted=OR 1.41, 95% CI 1.07- 1.84). Similarly obstructed labor (adjusted OR=4.45, 95% CI 1.17-16.96) found to be significantly associated with 4.45 times higher risk in the first day of life for surviving infants.

Similar analysis was conducted for combination of bleeding symptoms. The adjusted odds of either nasal bleeding or bulging fontanel if babies had obstructed delivery versus if babies did not have obstructed delivery was 2.65 (95% CI 1.38-5.09) in the first day of life, reflecting 2.65 times increased risk of either nasal bleeding or bulging fontanel significantly associated with obstructed delivery (Table 9.6A).

Table 9.6A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to obstructed delivery among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Obstructed labor 1st day																								
No	22117	2					22107	12	1				22025	94	1				22114	5	1			
Yes	4094	0					4091	3	1.35	0.24-5.0	1.49	0.41-5.36	4067	27	1.56	0.97-2.41	1.73	1.12-2.67	4090	4	4.32	0.86-20.09	4.45	1.17-16.96
2-7 days																								
No	22110	9					22113	6	1				21736	383	1				22090	29	1			
Yes	4094	0					4092	2	1.80	0.18-10.08	2.09	0.41-10.58	4014	80	1.13	0.88-1.45	1.21	0.94-1.55	4089	5	0.93	0.28-2.44	0.82	0.3[illegible]2.15
8 days-3mo																								
No	22104	15	1				22087	32	1				21830	289	1				22005	114	1			
Yes	4090	4	1.44	0.35-4.52	1.41	0.45-4.35	4089	5	0.84	0.26-2.18	0.86	0.33-2.23	4025	69	1.29	0.98-1.69	1.41	1.07-1.84	4074	20	0.95	0.56-1.53	0.91	0.5[illegible]1.48
3-6 mo																								
No	22067	52	1				22064	55	1				22114	5	1				21651	468	1			
Yes	4085	9	0.93	0.40-1.92	0.94	0.46-1.92	4087	7	0.69	0.26-1.51	0.68	0.30-1.49	4093	1	1.08	0.02-9.66	0.99	0.11-8.73	3996	98	1.13	0.90-1.42	0.90	0.6[illegible]1.19

	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical bleeding						Any Bleeding					
Obstructed labor 1st day	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
No	22105	14	1				22090	29	1				22012	107	1				21983	136	1			
Yes	4091	3	1.16	0.21-4.15	1.34	0.38-4.74	4080	14	2.61	1.27-5.12	2.65	1.38-5.09	4066	28	1.42	0.89-2.17	1.59	1.04-2.42	4055	39	1.55	1.06-2.24	1.66	1.16-2.39
2-7 days																								
No	22104	15	1				22090	29	1				21725	393	1				21685	434	1			
Yes	4092	2	0.72	0.08-3.1	0.81	0.18-3.61	4090	4	0.74	0.19-2.12	0.75	0.26-2.17	4013	81	1.12	0.87-1.42	1.20	0.94-1.54	4010	84	1.05	0.82-1.33	1.12	0.88-1.42
8 days-3mo																								
No	22072	47	1				22042	77	1				21787	332	1				21615	504	1			
Yes	4085	9	1.03	0.45-2.14	1.02	0.49-2.11	4076	18	1.26	0.71-2.13	1.18	0.69-1.98	4017	77	1.26	0.97-1.62	1.35	1.05-1.74	3984	110	1.18	0.95-1.46	1.21	0.98-1.49
3-6 mo																								
No	22012	107	1				21917	202	1				22007	112	1				21317	802	1			
Yes	4078	16	0.81	0.45-1.37	0.79	0.47-1.36	4056	38	1.02	0.70-1.45	0.92	0.64-1.30	4077	17	0.82	0.46-1.37	0.80	0.48-1.34	3933	161	1.09	0.91-1.29	0.91	0.75-1.10

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity and religion

Table 9.6B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to obstructed delivery among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Obstructed labor 1st day																								
No	2379	59	1				2390	48	1				2364	74	1				2438	0				
Yes	456	18	1.59	0.87-2.77	13.40	3.04-59.13	462	12	1.29	0.62-2.49	4.31	0.91-20.45	454	20	1.41	0.80-2.36	1.44	0.48-4.38	472	2				
2-7 days																								
No	2368	70	1				2425	13	1				2362	76	1				2431	7	1			
Yes	465	9	0.65	0.29-1.33	0.96	0.28-3.30	471	3	1.19	0.22-4.35	1.37	0.29-6.44	460	14	0.95	0.49-1.70	0.90	0.40-2.04	473	1	0.73	0.02-5.74	2.93	0.20-42.98
8 days-3mo																								
No	2409	29	1				2426	12	1				2412	26	1				2413	25				
Yes	466	8	1.43	0.56-3.22	1.84	0.80-4.23	473	1	0.43	0.01-2.90	0.70	0.09-5.72	471	3	0.59	0.11-1.94	0.89	0.26-3.04	471	3	0.61	0.12-2.03	1.43	0.35-5.48
3-6 mo																								
No	2435	3					2436	2					2438	0					2431	7	1			
Yes	474	0					474	0					474	0					473	1	0.73	0.02-5.74	3.66	0.31-43.92

	Nasal bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical bleeding						Any Bleeding					
Obstructed labor 1st day	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
No	2337	101	1				2357	81	1				2273	165	1				2256	182	1			
Yes	445	29	1.51	0.95-2.33	13.74	3.02-62.39	448	26	1.69	1.03-2.69	4.23	1.28-13.93	426	48	1.56	1.08-2.19	3.12	1.35-7.17	419	55	1.63	1.16-2.25	2.76	1.27-6.02
2-7 days																								
No	2357	81	1				2352	86	1				2289	149	1				2259	179	1			
Yes	462	12	0.76	0.37-1.41	0.67	0.19-2.26	462	12	0.71	0.35-1.32	1.04	0.39-2.74	449	25	0.88	0.44-1.76	0.83	0.42-1.66	444	30	0.85	0.55-1.28	0.86	0.47-1.59
8 days-3mo																								
No	2397	41	1				2389	49	1				2375	63	1				2320	118	1			
Yes	466	8	1.0	0.40-2.18	1.35	0.61-3.01	460	14	1.48	0.75-2.76	1.57	0.79-3.08	463	11	0.89	0.42-1.73	1.31	0.66-2.59	455	19	0.82	0.47-1.36	1.05	0.61-1.83
3-6 mo																								
No	2434	4					2428	10					2434	4					2418	20	1			
Yes	474	0					474	0					474	0					473	1	0.26	0.006-1.61	0.47	0.06-3.62

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity and religion

Adjusted analysis with either nasal bleeding, bruising or umbilical bleeding in the first day of life showed that obstructed delivery was significantly associated with 59% higher risk of such combination of bleeding (adjusted OR 1.59, 95% CI 1.02-2.42). Similarly, for any bleeding in the first day of life obstructed delivery was significantly associated with 66% higher risk of bleeding (adjusted OR= 1.66, 95% CI 1.16-2.39).

When similar analysis was conducted for the cohort of the deceased infants, the crude odds of any nasal bleeding if babies had obstructed delivery relative to if babies did not have obstructed delivery was 1.59 (95% CI 0.87-2.77) in the first day of life, reflecting nasal bleeding was not significantly associated with obstructed delivery, but when the odds ratio was adjusted, obstructed delivery was significantly associated with 13.40 times increased risk of nasal bleeding for deceased infants (adjusted OR= 13.40, 95% CI 3.04-59.13) in the first day of life (Table 9.6B).

When analysis was done to measure the association between obstructed delivery and combination of bleeding symptoms of the cohorts of the deceased infants, the adjusted odds of either nasal bleeding or bruising associated with if babies had obstructed delivery relative to if babies did not have obstructed delivery was 13.74 (95% CI 3.02-62.39) in the first day of life, reflecting 13.74 times increased risk any nasal bleeding or bruising significantly associated with obstructed delivery. The adjusted odds of either nasal bleeding or bulging fontanel if babies had obstructed delivery versus if babies did not have obstructed delivery was 4.23 (95% CI 1.28-13.93) in the first day of life, reflecting 4.23 times increased risk any nasal bleeding or bulging fontanel significantly associated with obstructed delivery.

Similar analysis with either nasal bleeding, bruising or umbilical bleeding in the first day of life showed, obstructed delivery was significantly associated with 3.12 times higher risk of such combination of bleeding (adjusted OR= 3.12, 95% CI 1.35-7.17). Similar analysis with any bleeding in the first day of life showed, obstructed delivery was significantly associated with 2.76 times higher risk of any bleeding (adjusted OR =2.76, 95% CI 1.27-6.02 for deceased infants (Table 9.6B).

9.7 Association between Religion and Bleeding Status among Cohorts of Surviving and Deceased Infants

The relationship between religion and risk of individual and combined bleeding symptoms were similarly examined separately among both the cohorts of surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between religion and onset of bleeding at each sequential age for both surviving (Table 9.7A) and deceased (Table 9.7B) infants separately. For assessing the independent effect of religion on bleeding symptoms the odds ratios of religion were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, morbidities, maternal age, parity and obstructed delivery.

When analysis for cohort of surviving infants was done, the adjusted odds of bruising if born in Hindu families relative to if born in Muslim families was 4.91(95% CI 1.52-15.86) in the first day of life, reflecting 4.91 times higher risk of bruising significantly associated with babies being born in Muslim families for surviving infants (Table 9.7A). Similar analysis for combination of bleeding symptoms was done.

Table 9.7A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to religion among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Religion																								
1st day																								
Islam	24514	2					24504	12	1				24408	108	1				24509	7	1			
Hinduism	2105	0					2101	4	3.89	0.91-12.8	4.91	1.52-15.86	2091	14	1.51	0.79-2.65	1.61	0.91-2.82	2103	2	3.33	0.34-17.50	3.52	0.70-17.68
2-7 days																								
Islam	24508	8					24508	8					24078	438	1				24482	34	1			
Hinduism	2105	0					2105	0					2077	28	0.74	0.49-1.09	0.82	0.56-1.21	2104	1	0.34	0.01-2.04	0.39	0.05-2.92
8 days-3mo																								
Islam	24499	17	1				24480	36					24180	336	1				24385	131	1			
Hinduism	2103	2	1.37	0.15-5.78	1.54	0.35-6.78	2105	0					2075	30	1.04	0.69-1.52	1.19	0.81-1.75	2101	4	0.35	0.09-0.93	0.39	0.15-1.08
3-6 mo																								
Islam	24459	57	1				24462	54	1				24511	5	1				23984	532	1			
Hinduism	2100	5	1.02	0.32-2.53	1.04	0.41-2.59	2097	8	1.73	0.71-3.66	1.77	0.84-3.75	2104	1	2.33	0.05-20.83	2.13	0.25-18.56	2070	35	0.76	0.52-1.08	0.84	0.57-1.26

	Nasal bleeding / Bruising						Nasal bleeding / Bulging Fontanel						Nasal bleeding / Bruising / Umbilical bleeding						Any Bleeding					
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
1st day																								
Islam	24502	14	1				24473	43					24396	120	1				24356	160	1			
Hinduism	2101	4	3.33	0.79-10.62	4.17	1.32-13.13	2105	0					2088	17	1.66	0.93-2.77	1.78	1.06-2.99	2088	17	1.24	0.70-2.05	1.29	0.78-2.14
2-7 days																								
Islam	24500	16					24485	31	1				24068	448	1				24027	489	1			
Hinduism	2105	0					2104	1	0.38	0.01-2.26	0.42	0.06-3.06	2077	28	0.72	0.47-1.06	0.81	0.55-1.19	2073	32	0.76	0.51-1.09	0.84	0.58-1.21
8 -3 mo																								
Islam	24463	53	1				24426	90	1				24131	385	1				23930	586	1			
Hinduism	2103	2	0.44	0.05-1.67	0.49	0.12-2.00	2099	6	0.78	0.28-1.78	0.83	0.36-1.89	2074	31	0.94	0.63-1.36	1.07	0.73-1.56	2067	38	0.75	0.52-1.05	0.83	0.59-1.16
3-6 mo																								
Islam	24405	111	1				24285	231	1				24400	116	1				23612	904	1			
Hinduism	2092	13	1.37	0.70-2.44	1.39	0.78-2.49	2093	12	0.60	0.31-1.08	0.62	0.34-1.10	2091	14	1.41	0.75-2.46	1.42	0.81-2.48	2040	65	0.83	0.63-1.08	0.86	0.65-1.14

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity and obstructed labor

Table 9.7B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to religion among deceased infants

	Nasal bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Religion																								
1st day																								
Islam	2788	73	1				2802	59	1				2764	97	1				2859	2				
Hinduism	259	6	0.88	0.31-2.05	2.32	0.76-7.09	262	3	0.54	0.11-1.69			260	5	0.55	0.17-1.34	0.52	0.07-3.94	265	0				
2-7 days																								
Islam	2790	71	1				2845	16					2775	86	1				2852	9	1			
Hinduism	254	11	1.70	0.80-3.28	1.84	0.61-5.51	265	0					257	8	1.00	0.42-2.10	1.13	0.47-2.71	264	1	1.20	0.03-8.72		
8 days-3mo																								
Islam	2828	33	1				2848	13					2835	26	1				2835	26	1			
Hinduism	261	4	1.31	0.34-3.73			265	0					260	5	2.09	0.62-5.61	1.83	0.64-5.48	263	2	0.83	0.09-3.34		
3-6 mo																								
Islam	2858	3					2859	2					2861	0					2853	8				
Hinduism	265	0					265	0					265	0					265	0				

	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical bleeding						Any Bleeding					
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
1st day																								
Islam	2736	125	1				2760	101	1				2651	210	1				2629	232	1			
Hinduism	256	9	0.77	0.34-1.53			256	9	0.96	0.42-1.93	2.78	1.16-6.59	251	14	0.70	0.37-1.23	0.46	0.06-3.51	248	17	0.78	0.44-1.29	0.38	0.05-2.88
2-7 days																								
Islam	2776	85	1				2772	89	1				2699	162	1				2663	198	1			
Hinduism	254	11	1.41	0.67-2.70	1.66	0.56-4.94	250	15	1.87	0.98-3.31	1.57	0.64-3.82	247	18	1.21	0.69-2.02	1.26	0.61-2.64	243	22	1.22	0.73-1.94	1.24	0.64-2.42
8 -3 mo																								
Islam	2816	45	1				2804	57	1				2794	67	1				2735	126	1			
Hinduism	261	4	0.96	0.25-2.66	1.23	0.43-3.58	259	63	1.14	0.39-2.67	3.06	0.61-15.32	256	9	1.47	0.63-2.99	1.66	0.76-3.64	252	13	1.12	0.57-2.02	1.41	0.63-2.30
3-6 mo																								
Islam	2857	4					2853	8	1				2857	4					2842	19	1			
Hinduism	265	0					263	2	2.71	0.28-13.68			265	0					263	2	1.14	0.13-4.76	1.56	0.34-7.18

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, morbidities, maternal age, maternal parity and obstructed labor

The adjusted odds of either nasal bleeding, bruising if babies born in Hindu families versus if babies born in Muslim families was 4.17 (95% CI 1.32-13.13) in the first day of life, indicating a 4.17 times increased risk of either nasal bleeding or bruising significantly associated with babies being born in Muslim families.

Similar analysis with nasal bleeding, bruising or umbilical bleeding in the first day of life showed, babies being born in Muslim families was significantly associated with 78% higher risk of such combination of bleeding (OR 1.78, 95% CI 1.06-2.99) for surviving infants.

When analysis for the cohort of deceased infants was done, the adjusted odds of nasal bleeding if babies born in Hindu families relative to if babies born in Muslim families was 2.32 (95% CI 0.76-7.09) at 2 days to 7 days of age, reflecting 2.32 times risk of nasal bleeding non-significantly associated with babies born in Muslim families. The adjusted odds of umbilical bleeding if babies born in Hindu families versus if babies born in Muslim families was 1.13 (95% CI 0.47-2.71) at 2days to 7 days of age, indicating a 13% increased risk of umbilical bleeding non-significantly associated with babies born in Muslim families. Similar analysis with at 8 days to 3 months of life showed, babies born in Muslim families had 83% non-significant higher risk of having umbilical bleeding (adjusted OR =1.83, 95% CI 0.61-5.48) for deceased infants (Table 9.7B).

When analysis was done for combination of bleeding symptoms, the adjusted odds of either nasal bleeding or bulging fontanel if babies born in Hindu families relative to if babies born in Muslim families was 2.78 (95% CI 1.16-6.59) in the first day of life, reflecting 2.78 times increased risk of either nasal bleeding or bulging fontanel significantly associated with babies born in Muslim families for deceased infants (Table 9.7B).

9.8 Association between Cough and Bleeding Status among Cohort of Surviving and Deceased Infants

The relationship between cough and risk of individual and combined bleeding symptoms were examined separately among both the cohorts of surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Mothers were asked whether their surviving infants suffered from cough/cold in last 3 months during the 6 months follow up interviews. On the other hand, mothers were asked whether their deceased infants had cough/cold in the 7days of deaths during the verbal autopsies. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between cough and onset of bleeding at each sequential age for both surviving (Table 9.8A) and deceased (Table 9.8B) infants separately. For assessing the independent effect of cough on bleeding symptoms the odds ratios of cough were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed delivery and religion.

When analysis was done for the cohort of surviving infants, the adjusted odds of umbilical bleeding if babies had cough in last 3 months relative to the odds of umbilical bleeding if they did not have cough was 2.75 (95% CI 1.27-5.98) in the first day of life, indicating a 2.75 times higher risk of umbilical bleeding significantly associated with cough in last 3 months for surviving infants (Table 9.8A). The crude odds of umbilical bleeding if babies had cough in last 3 months versus if they did not have cough was 1.44 (95% CI 1.06-2.00) at 2 days to 7 days of age, reflecting 44% higher risk of umbilical bleeding significantly associated with cough in last 3 months. But when the odds ratio was adjusted, the association became statistically non-significant (adjusted OR=1.34, 95% CI 0.98-1.85).

Similar adjusted analysis with umbilical bleeding for 8 days to 3 months of age showed, cough in last 3 months was significantly associated with 2.18 times higher risk of umbilical bleeding (adjusted OR =2.18, 95% CI 1.40- 3.39). Similar analysis with fresh intestinal bleeding for 2 days to 7 days of age showed, cough was significantly associated with 68% lower risk of fresh bleeding (adjusted OR= 0.32, 95% CI 0.14- 0.75). Similar analysis was done for combined bleeding symptoms with cough in the last 3 months for surviving infants (Table 9.8A). The adjusted odds of either nasal bleeding or bulging fontanel associated with if babies had cough in last 3 months relative to if they did not have cough was 1.72 (95% CI 1.01-2.95) at 3 months to 6 months of age, reflecting a 72% higher risk of either nasal bleeding or bulging fontanel associated with cough in last 3 months.

Table 9.8A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to cough in last 3 months among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI
	No	Yes					No	Yes					No	Yes					No	Yes				
Cough																								
1st day																								
No	3569	0					3566	3	1				3562	7	1				3569	0				
Yes	22850	2					22839	13	0.68	0.19-3.70	1.13	0.24-5.26	22737	115	2.57	1.21-6.55	2.75	1.27-5.98	22843	9				
2-7 days																								
No	3569	0					3569	0					3523	46	1				3561	8	1			
Yes	22843	9					22844	8					22430	422	1.44	1.06-2.00	1.34	0.98-1.85	22825	27	0.53	0.23-1.34	0.32	0.14-0.75
8 days-3mo																								
No	3568	1	1				3565	4	1				3546	23	1				3554	15	1			
Yes	22834	18	2.81	0.44-117.19	2.04	0.26-15.98	22820	32	1.25	0.44-4.87	0.85	0.29-2.51	22509	343	2.35	1.54-3.76	2.18	1.40-3.39	22732	120	1.25	0.73-2.31	0.85	0.48-1.49
3-6 mo																								
No	3562	7	1				3566	3	1				3568	1	1				3513	56	1			
Yes	22797	55	1.23	0.55-3.19	1.09	0.49-2.48	22793	59	3.08	1.00-15.35	2.97	0.91-9.67	22847	5	0.78	0.09-36.93	0.85	0.09-7.92	22338	514	1.44	1.09-1.94	0.88	0.63-1.23

	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical Bleeding						Any Bleeding					
Cough																								
1st day																								
No	3566	3	1				3564	5	1				3559	10	1				3553	16	1			
Yes	22837	15	0.78	0.22-4.21	1.47	0.32-6.69	22814	38	1.19	0.47-3.87	1.19	0.46-3.13	22725	127	1.99	1.05-4.25	2.44	1.22-4.86	22691	161	1.57	0.94-2.83	1.83	1.06-3.15
2-7 days																								
No	3569	0					3566	3	1				3523	46	1				3511	58	1			
Yes	22835	17					22822	30	1.56	0.49-8.00	1.19	0.35-4.08	22419	433	1.48	1.09-2.06	1.38	1.01-1.89	22385	466	1.26	0.95-1.69	1.15	0.86-1.53
8 days-3mo																								
No	3564	5	1				3565	4	1				3541	28	1				3521	48	1			
Yes	22807	50	1.56	0.63-5.03	1.08	0.42-2.81	22760	92	3.60	1.36-13.51	2.49	0.89-6.90	22464	388	2.18	1.48-3.34	1.96	1.31-2.92	22276	576	1.89	1.41-2.61	1.58	1.16-2.15
3-6 mo																								
No	3559	10	1				3554	15	1				3558	11	1				3486	83	1			
Yes	22708	114	1.78	0.93-3.82	1.66	0.85-3.23	22624	221	2.39	1.42-4.34	1.72	1.01-2.95	22733	119	1.69	0.91-3.49	1.59	0.84-2.99	21963	889	1.70	1.35-2.16	1.22	0.95-1.57

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

Table 9.8B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to cough in 7 days of deaths among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						Fresh Intestinal Bleeding					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Cough																								
1st day																								
No	742	4	1				741	5	1				733	13	1				745	1	1			
Yes	875	5	1.06	0.23-5.36	0.85	0.18-3.98	878	2	0.34	0.03-2.07	0.29	0.05-1.82	866	14	0.91	0.39-2.12	0.60	0.25-1.46	879	1	0.85	0.01-66.62	0.89	0.06-14.26
2-7 days																								
No	717	29	1				738	8	1				708	38	1				745	1	1			
Yes	866	14	0.40	0.19-0.79	0.68	0.27-1.67	876	4	0.42	0.09-1.58	0.32	0.09-1.21	844	36	0.79	0.48-1.30	0.73	0.41-1.29	872	8	6.83	0.91-303.63	4.76	0.32-70.23
8 days-3mo																								
No	727	19	1				743	3	1				734	12	1				740	6	1			
Yes	863	17	0.75	0.37-1.54	0.59	0.27-1.27	873	7	1.98	0.45-11.94	2.78	0.62-12.71	862	18	1.28	0.58-2.93	1.31	0.54-3.22	858	22	3.16	1.23-9.57	2.72	0.90-9.18
3-6 mo																								
No	744	2	1				746	0					746	0					744	2	1			
Yes	879	1	0.42	0.01-8.15	0.25	0.02-3.38	878	2					880	0					874	6	2.55	0.45-25.93	3.28	0.45-23.66
Cough	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical Bleeding**						**Any Bleeding**					
1st day																								
No	738	8	1				739	7	1				728	18	1				726	20	1			
Yes	873	7	0.74	0.23-2.35	0.45	0.09-2.17	869	11	1.36	0.47-4.09	1.01	0.29-3.63	860	20	0.94	0.47-1.90	0.65	0.29-1.46	856	24	1.02	0.53-1.96	0.72	0.34-1.53
2-7 days																								
No	710	36	1				709	37	1				677	69	1				664	82	1			
Yes	862	18	0.41	0.22-0.75	0.52	0.23-1.16	853	27	0.61	0.35-1.03	0.90	0.44-1.85	830	50	0.59	0.39-0.88	0.65	0.39-1.07	808	72	0.72	0.51-1.02	0.77	0.49-1.19
8 days-3mo																								
No	724	22	1				718	28	1				714	32	1				695	51	1			
Yes	857	23	0.88	0.47-1.68	0.79	0.39-1.56	846	34	1.03	0.60-1.78	0.77	0.42-1.39	841	39	1.03	0.62-1.73	0.87	0.49-1.54	797	83	1.42	0.97-2.08	1.24	0.80-1.91
3-6 mo																								
No	744	2	1				741	5	1				744	2	1				738	8	1			
Yes	878	2	0.85	0.06-11.71	0.47	0.06-4.06	875	5	0.85	0.19-3.69	0.61	0.15-2.52	878	2	0.85	0.61-11.71	0.47	0.06-4.06	867	13	1.38	0.53-3.87	1.02	0.36-2.87

*adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

The adjusted odds of nasal bleeding, bruising or umbilical bleeding associated with if babies had cough in last 3 months relative to if they did not have cough was 1.38 (95% CI 1.01-1.89) for 2 days to 7 days of age indicating a 38% higher risk of either nasal bleeding, bruising or umbilical bleeding significantly associated with cough in the past 3 months. Same pattern persisted for 3 months to 6 months of age, cough being significantly associated with 97% higher risk of nasal bleeding, bruising or umbilical bleeding (adjusted OR= 1.97, 95% CI 1.32-2.94). Similar direction of increased risk persisted for any bleeding (adjusted OR= 1.83, 95% CI 1.06-3.15) in the first day of life and for 8 days to 3 months of age (adjusted OR= 1.58, 95% CI 1.16-2.15).

When analyzed for the cohort of deceased infants, the crude odds of nasal bleeding found to be if babies had cough within 7 days of death relative to if they did not have cough was 0.40 (95% CI 0.19-0.79) at 2 days to 7 days of age, reflecting a 60% lower risk of nasal bleeding significantly associated with cough within 7 days of death. But, when the odds ratio was adjusted, the association became non-significant (adjusted OR=0.68, 95% CI 0.27-1.67) for deceased infants (Table 9.8 B). The crude odds of fresh intestinal bleeding if babies had cough within 7 days of death versus if they did not have cough was 3.16 (95% CI 1.23-9.57) at 3 months to 6 months of age, reflecting a 3.16 times higher risk of fresh intestinal bleeding significantly associated with cough in 7 days of death. When the odds ratio was adjusted, the association became non-significant (adjusted OR=2.72, 95% CI 0.90-8.18) for deceased infants.

For combination of bleeding symptoms, the crude odds of either nasal bleeding, bruising or umbilical bleeding if babies had cough in 7 days of deaths relative to if they did not have cough was 0.59 (95% CI 0.39-0.88) at 2 days to 7 days of age, reflecting a 41% significant lower risk of either nasal bleeding, bruising or umbilical bleeding associated with cough in 7 days of deaths for deceased infants. But when the odds ratio was adjusted the association became non-significant (adjusted OR=0.64, 95% CI 0.39-1.05).

9.9 Association between High Fever and Bleeding Status among Cohort of Surviving Infants

The relationship between high fever and risk of individual and combined bleeding symptoms were examined among cohort of surviving infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Mothers were asked whether their surviving infants suffered from high fever in last 3 months during the 6 months follow up interviews. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between high fever and onset of bleeding at each sequential age for surviving infants (Table 9.9). For assessing the independent effect of high fever on bleeding symptoms, the odds ratios of high fever were adjusted by logistic regression for gender, maturity, number of siblings, colostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed delivery and religion.

Table 9.9: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to high fever in last 3 months among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
High fever																								
1st day																								
No	10614	2					10608	8	1				10566	50	1				10611	5	1			
Yes	15799	0					15791	8	0.67	0.22-2.05	0.79	0.27-2.26	15727	72	0.97	0.66-1.42	0.86	0.59-1.25	15795	4	0.54	0.11-2.49	0.32	0.08-1.27
2-7 days																								
No	10614	2	1				10614	2	1				10446	170	1				10606	10	1			
Yes	15792	7	2.35	0.45-23.21	2.27	0.46-11.11	15793	6	2.02	0.36-20.43	2.09	0.42-10.45	15501	298	1.18	0.97-1.44	1.00	0.82-1.23	15774	25	1.68	0.78-3.92	1.49	0.66-3.39
8-3 mo																								
No	10611	5	1				10606	10	1				10496	120	1				10583	33	1			
Yes	15786	14	1.88	0.64-6.68	1.41	0.48-4.08	15772	23	1.82	0.85-4.21	1.59	0.72-3.54	15554	245	1.38	1.10-1.73	1.14	0.91-1.43	15697	102	2.08	1.39-3.19	1.55	1.02-2.35
3-6 mo																								
No	10595	21	1				10592	24	1				10613	3	1				10480	136	1			
Yes	15758	41	1.31	0.76-2.34	1.38	0.79-2.40	15761	38	1.06	0.62-1.86	1.03	0.60-1.77	15796	3	0.67	0.09-5.02	0.69	0.13-3.67	15365	434	2.18	1.78-2.66	1.30	1.03-1.64
High fever	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical bleeding**						**Any Bleeding**					
1st day																								
No	10606	10	1				10597	19	1				10557	59	1				10538	79	1			
Yes	15791	8	0.54	0.18-1.51	0.59	0.22-1.58	15775	24	0.85	0.45-1.64	0.80	0.43-1.49	15721	78	0.89	0.62-1.27	0.82	0.58-1.17	15700	99	0.85	0.63-1.16	0.79	0.58-1.08
2-7 days																								
No	10612	4	1				10607	9	1				10443	173	1				10428	188	1			
Yes	15786	13	2.18	0.67-9.19	2.24	0.72-0.95	15775	24	1.79	0.80-4.38	1.51	0.68-3.37	15493	306	1.19	0.98-1.45	1.01	0.83-1.23	15463	336	1.21	1.00-1.45	1.06	0.87-1.28
8-3 mo																								
No	10601	15	1				10594	22	1				10481	135	1				10426	190	1			
Yes	15758	41	1.84	0.99-3.58	1.51	0.79-2.87	15725	74	2.27	1.39-3.83	1.84	1.11-3.02	15518	281	1.41	1.14-1.74	1.17	0.94-1.46	15265	434	1.55	1.30-1.85	1.27	1.06-1.52
3-6 mo																								
No	10571	45	1				10563	53	1				10568	48	1				10363	253	1			
Yes	15720	79	1.18	0.81-1.74	1.19	0.81-1.75	15609	190	2.43	1.78-3.36	2.19	1.59-3.00	15717	82	1.15	0.79-1.68	1.16	0.79-1.69	15080	719	1.95	1.68-2.26	1.44	1.22-1.69

* adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

The adjusted odds of fresh intestinal bleeding if babies had high fever in the past 3 months relative to if they did not have high fever was 1.55 (95% CI 1.02-2.26) at 8 days to 3 months of life, indicating a 55% higher risk of fresh intestinal bleeding associated with high fever in last 3 months. Similar analysis with fresh intestinal bleeding for 3 months to 6 months of age showing high fever in the last 3 months was significantly associated with 30% higher risk of fresh intestinal bleeding (adjusted OR= 1.30, 95% CI 1.03-1.64).

For combination of bleeding at 8 days to 3 months, high fever in last 3 months (adjusted OR=1.84, 95% CI 1.11-3.02) was significantly associated with a 84% higher risk of either nasal bleeding or bulging fontanel. Similar pattern existed for 3 months to 6 months of age (adjusted OR= 2.19, 95% CI 1.59-3.00). Similarly high fever in last 3 months was significantly associated with (adjusted OR1.27, 95% CI 1.06-1.52) 27% higher risk of any bleeding at 8 days to 3 months. For 3 months to 6 months of age also, it was significantly associated with a 44% higher risk of any bleeding (adjusted OR= 1.44, 95% CI 1.22-1.69).

9.10 Association between Breathing Difficulties and Bleeding Status among Cohort of Deceased Infants

The relationship between breathing difficulties and risk of individual and combined bleeding symptoms were examined among the cohort of deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Mothers were asked during the verbal autopsies whether their deceased infants had breathing difficulties in the preceding 7 days prior to death.

Table 9.10: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to breathing difficulties in 7 days of deaths among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Breathing difficulties																								
1st day																								
No	716	2	1				715	3	1				713	5	1				718	0				
Yes	901	7	2.78	0.53-27.5	3.02	0.50-18.22	904	4	1.05	0.18-7.22	1.78	0.34-9.39	886	22	3.54	1.29-12.02	4.93	1.55-15.69	906	2				
2-7 days																								
No	652	26	1				713	5	1				683	35	1				717	1	1			
Yes	891	17	0.51	0.26-0.98	0.55	0.22-1.39	901	7	1.11	0.30-4.45	1.82	0.51-6.45	869	39	0.88	0.53-1.44	1.05	0.59-1.88	900	8	6.37	0.85-283.14	2.18	0.63-23.68
8 3 mo																								
No	702	16	1				713	5	1				705	13	1				706	12	1			
Yes	887	21	1.04	0.51-2.15	1.39	0.64-3.00	903	5	0.79	0.18-3.45	0.45	0.11-1.79	891	17	1.03	0.47-2.33	0.96	0.39-2.38	892	16	1.06	0.46-2.46	0.44	0.16-1.21
3-6 mo																								
No	717	1	1				718	0					718	0					716	2	1			
Yes	906	2	1.58	0.08-93.49	2.04	0.15-27.94	906	2					908	0					902	6	2.38	0.42-24.18	0.59	0.13-4.27
Breathing difficulties	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical Bleeding**						**Any Bleeding**					
1st day																								
No	713	5	1				713	5	1				709	9	1				707	11	1			
Yes	898	10	1.59	0.49-5.95	2.70	0.61-22.59	895	13	2.07	0.69-7.45	2.73	0.63-11.81	879	29	2.59	1.19-6.28	3.86	1.44-10.36	875	33	2.42	1.18-5.35	3.18	1.32-7.65
2-7 days																								
No	688	30	1				687	31	1				656	62	1				647	71	1			
Yes	884	24	0.62	0.35-1.11	0.70	0.31-1.57	875	33	0.84	0.49-1.43	0.80	0.39-1.65	851	57	0.71	0.48-1.05	0.85	0.52-1.39	825	83	0.92	0.65-1.29	0.96	0.62-1.49
8-3 mo																								
No	697	21	1				693	25	1				687	31	1				661	57	1			
Yes	883	25	0.94	0.50-1.78	1.05	0.53-2.08	870	38	1.21	0.70-2.11	1.45	0.78-2.68	867	41	1.05	0.63-1.75	1.11	0.63-1.96	830	78	1.09	0.75-1.59	0.92	0.59-1.42
3-6 mo																								
No	717	1	1				714	4	1				717	1	1				711	7	1			
Yes	905	3	2.38	0.19-124.93	2.69	0.22-32.28	902	6	1.18	0.28-5.74	1.29	0.15-5.46	905	3	2.38	0.19-124.93	2.69	0.22-32.28	894	14	1.59	0.59-4.68	0.96	0.33-2.80

* adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

Crude and adjusted odd ratios with 95% CI were calculated to assess the association between breathing difficulties and onset of bleeding at each sequential age (Table 9.10) for deceased infants. For assessing the independent effect of breathing difficulties on bleeding symptoms, the odds ratios of breathing difficulties were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed delivery and religion.

When analyzed, the association between breathing difficulties in the preceding 7 days prior to death with bleeding symptoms for deceased infants, the adjusted odds of umbilical bleeding was found to be associated with if babies having breathing difficulties in 7 days prior to death. Comparing with infants not having breathing difficulties, the odds was 4.93 (95% CI 1.55-15.69) in the first day of life, indicating a 4.93 times higher risk of umbilical bleeding significantly associated with breathing difficulties in 7 days of deaths of deceased infants.

The adjusted odds of either nasal bleeding, bruising or umbilical bleeding if babies had breathing difficulties within 7 days of death versus if did not have breathing difficulties was 3.86 (95% CI 1.44-10.36) in the first day of life, reflecting 3.86 times higher risk of either nasal bleeding, bruising or umbilical bleeding being significantly associated with breathing difficulties within 7 days of deaths (Table 9.10). Similar analysis with any bleeding showed breathing difficulties in last 7 days of deaths being significantly associated with 3.18 times higher risk of any bleeding in the first day of life of deceased infants (adjusted OR=3.18, 95% CI 1.32-7.65).

9.11 Association between Diarrhoea and Bleeding Status among Cohorts of Surviving and Deceased Infants

The relationship between diarrhoea and risk of individual and combined bleeding symptoms were examined separately among both the cohorts of surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Mothers were asked whether their surviving infants suffered from diarrhoea in the last 3 months during the 6-month follow up interviews. On the other hand, mothers were asked whether their deceased infants suffered from diarrhoea in the 7 days of deaths during the verbal autopsies. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between diarrhoea and onset of bleeding at each sequential age for both cohorts of surviving (Table 9.11A) and deceased (Table 9.11B) infants separately. For assessing the independent effect of diarrhoea on bleeding symptoms the odds ratios for diarrhoea were adjusted by logistic regression for gender, maturity at birth, number of siblings, colostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed delivery and religion.

When analyzed for cohort of surviving infants, the adjusted odds of bruising for babies who had diarrhoea in the last 3 months relative to who did not have diarrhoea was 3.06 (95% CI 1.53-6.12) at 8 days to 3 months of age, indicating a 3.06 times higher risk of bruising found to be significantly associated with diarrhoea in last 3 months for surviving infants (Table 9.11A).

The adjusted odds of umbilical bleeding associated if babies had diarrhoea in last 3 months versus if they did not have diarrhoea was 1.43 (95% CI 1.15-1.79) at 2 days to 7 days of age, reflecting a 43% higher risk of umbilical bleeding being significantly associated with diarrhoea in last 3 months. Similar analysis with umbilical bleeding for 8 days to 3 months of age showed, diarrhoea in last 3 months was significantly associated with a 57% higher risk of umbilical bleeding (adjusted OR= 1.57, 95% CI 1.23- 2.00). For combination of bleeding symptoms, the adjusted odds of either nasal bleeding or bruising if babies had diarrhoea in last 3 months relative to if they did not have diarrhoea was 2.79 (95% CI 1.58-4.93) at 8 days to 3 months of age, reflecting a 2.79 times higher risk of either nasal bleeding or bruising associated with diarrhoea in last 3 months for surviving infants (Table 9.11A).

Similar pattern of increased risk was found for either nasal bleeding or bulging fontanel (adjusted OR= 2.48 (95% CI 1.17-5.22) at 2 days to 7 days and for 3 months to 6 months of age (adjusted OR= 2.38, 95% CI 1.54-3.68) for diarrhoea in surviving infants.

The adjusted odds of either nasal bleeding, bruising or umbilical bleeding if babies had diarrhoea in last 3 months relative to if they did not have diarrhoea was 1.41 (95% CI 1.13-1.77) at 2 days to 7 days of age, indicating a 41% higher risk of nasal bleeding, bruising or umbilical bleeding associated with diarrhoea in last 3 months. Similar analysis with nasal bleeding, bruising or umbilical bleeding up to 3 months of age showed, diarrhoea in last 3 months was significantly associated with 41-66% higher risk of bleeding.

Table 9.11A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to diarrhoea in last 3 months among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI			OR	95%CI	OR	95%CI
	No	Yes					No	Yes					No	Yes					No	Yes				
Diarrhoea																								
1st day																								
No	22148	2					22136	14	1				22041	109	1				22143	7	1			
Yes	4266	0					4264	2	0.74	0.08-3.23	0.86	0.19-3.89	4253	13	0.62	0.32-1.10	0.56	0.31-1.00	4264	2	1.48	0.15-7.79	1.16	0.23-5.89
2-7 days																								
No	22143	7	1				22143	7	1				21790	360	1				22125	25	1			
Yes	4264	2	1.48	0.15-7.79	1.16	0.24-5.71	4265	1	0.74	0.02-5.78	0.64	0.08-5.27	4158	108	1.57	1.25-1.96	1.43	1.15-1.79	4256	10	2.08	0.89-4.48	1.29	0.59-2.78
8 days-3mo																								
No	22137	13	1				22127	23	1				21879	271	1				22049	101	1			
Yes	4260	6	2.39	0.75-6.76	2.32	0.85-6.30	4252	14	3.17	1.51-6.43	3.06	1.53-6.12	4171	95	1.84	1.44-2.34	1.57	1.23-2.00	4232	34	1.75	1.15-2.61	1.16	0.77-1.74
3-6 mo																								
No	22096	54	1				22102	48	1				22145	5	1				21741	409	1			
Yes	4258	8	0.77	0.32-1.62	0.73	0.35-1.55	4252	14	1.52	0.77-2.79	1.52	0.83-2.79	4265	1	1.04	0.02-9.28	1.16	0.13-10.17	4105	161	2.08	1.72-2.52	1.06	0.85-1.32
Diarrhoea	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical Bleeding**						**Any Bleeding**					
1st day																								
No	22134	16	1				22114	36	1				22027	123	1				21995	155	1			
Yes	4264	2	0.65	0.07-2.76	0.74	0.17-3.39	4259	7	1.01	0.38-2.30	1.00	0.44-2.27	4252	14	0.59	0.31-1.03	0.55	0.32-0.97	4244	22	0.74	0.45-1.16	0.71	0.45-1.12
2-7 days																								
No	22136	14	1				22128	22	1				21780	370	1				21749	401	1			
Yes	4263	3	1.11	0.20-3.98	0.95	0.27-3.34	4255	11	2.60	1.14-5.60	2.48	1.17-5.22	4157	109	1.54	1.23-1.92	1.41	1.13-1.77	4143	123	1.61	1.30-1.98	1.48	1.19-1.83
8 days-3mo																								
No	22114	36	1				22086	64	1				21844	306	1				21689	461	1			
Yes	4246	20	2.89	1.59-5.14	2.79	1.58-4.93	4234	32	2.61	1.65-4.05	2.38	1.54-3.68	4155	111	1.91	1.52-2.38	1.65	1.31-2.08	4102	164	1.88	1.56-2.26	1.57	1.29-1.89
3-6 mo																								
No	22048	102	1				21954	196	1				22043	107	1				21435	715	1			
Yes	4244	22	1.12	0.67-1.79	1.09	0.69-1.76	4219	47	1.25	0.89-1.73	1.03	0.74-1.43	4243	23	1.12	0.68-1.77	1.14	0.73-1.79	4009	257	1.92	1.66-2.23	1.25	1.07-1.49

* adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

Table 9.11B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to diarrhoea in 7 days of deaths among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Diarrhoea																								
1st day																								
No	1504	9					1505	8					1487	26	1				1511	2				
Yes	235	0					235	0					234	1	0.24	0.01-1.50	0.26	0.03-1.96	235	0				
2-7 days																								
No	1463	50					1497	16					1442	71	1				1506	7	1			
Yes	235	0					235	0					226	9	0.81	0.35-1.65	0.97	0.45-2.11	232	3	2.78	0.46-12.28		
8 days-3mo																								
No	1478	35	1				1501	12	1				1485	28	1				1494	19	1			
Yes	233	2	0.36	0.04-1.43	0.35	0.08-1.49	234	1	0.53	0.01-3.65	0.53	0.06-4.38	232	3	0.69	0.13-2.25	0.42	0.09-1.83	226	9	3.13	1.23-7.37	1.39	0.44-4.01
3-6 mo																								
No	1512	1	1				1511	2					1513	0					1509	4	1			
Yes	233	2	12.97	0.67-766.09	14.19	1.20-167.73	235	0					235	0					231	4	6.53	1.21-35.26	6.37	1.01-40.25
Diarrhoea	**Nasal Bleeding / Bruising**						**Nasal Bleeding / Bulging Fontanel**						**Nasal Bleeding / Bruising / Umbilical Bleeding**						**Any Bleeding**					
1st day																								
No	1497	16					1495	18					1475	38	1				1469	44	1			
Yes	235	0					235	0					234	1	0.17	0.01-0.99	0.21	0.03-1.56	234	1	0.14	0.004-0.85	0.17	0.02-1.29
2-7 days																								
No	1449	64					1448	65	1				1387	126	1				1356	157	1			
Yes	235	0					229	6	0.58	0.20-1.36	0.77	0.27-2.25	226	9	0.44	0.19-0.88	0.67	0.32-1.44	218	17	0.67	0.38-1.14	0.74	0.39-1.39
8 days-3mo																								
No	1467	46	1				1455	58	1				1443	70	1				1392	121	1			
Yes	232	3	0.41	0.08-1.30	0.42	0.13-1.40	230	5	0.55	0.17-1.37	0.53	0.21-1.38	229	6	0.54	0.19-1.26	0.44	0.17-1.14	217	18	0.95	0.54-1.61	0.64	0.36-1.16
3-6 mo																								
No	1511	2	1				1508	5	1				1511	2	1				1502	11	1			
Yes	233	2	6.48	0.47-89.69	6.48	0.86-48.64	230	5	6.56	1.49-28.67	6.82	1.89-24.48	233	2	6.48	0.47-89.69	6.48	0.86-48.64	225	10	6.07	2.28-15.91	4.45	1.70-11.67

* adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

Similar pattern of increased risk significantly associated with diarrhoea was found for any bleeding (adjusted OR=1.48, 95% CI 1.19-1.83) at 2 days to 7 days, for 8 days to 3 months (adjusted OR= 1.57, 95% CI 1.29-1.89) and for 3 months to 6 months of age (adjusted OR= 1.26, 95% CI 1.07-1.49) for diarrhoea in surviving infants.

When similar analysis for the cohort of deceased infants was conducted, the adjusted odds of nasal bleeding for babies if they had diarrhoea in 7 days relative to if they did not have diarrhoea was 14.19 (95% CI 1.20-167.73) at 3 months to 6 months of age, indicating a 14.19 times higher risk of nasal bleeding found to be significantly associated with diarrhoea in 7 days of deaths for deceased infants (Table 9.11B). The adjusted odds of fresh intestinal bleeding if babies had diarrhoea in 7 days versus if they did not have diarrhoea was 6.37 (95% CI 1.01-40.25) at 3 months to 6 months of age, reflecting a 6.37 times higher risk of fresh intestinal bleeding being significantly associated with diarrhoea in 7 days of deaths.

When analyzed for combination of bleeding symptoms, diarrhoea being found to be significantly associated with any nasal bleeding or bulging fontanel (adjusted OR6.82, 95% CI 1.89-24.48) at 3 months to 6 months of age. Similar analysis with any bleeding for 3 months to 6 months of age showed, diarrhoea within 7 days of death was significantly associated with 4.45 times higher risk of any bleeding (adjusted OR= 4.45, 95% CI 1.70- 11.67) for deceased infants (Table 9.11B).

9.12 Association between Dysentery and Bleeding Status among Cohorts of Surviving and Deceased Infants

The relationship between dysentery and risk of individual and combined bleeding symptoms were examined separately among both the cohorts of surviving and deceased infants as a means of assessing the consistency in association and controlling for potential biases and confounders. Mothers were asked whether their surviving infants suffered from dysentery in the last 3 months during the 6 months follow up interviews. On the other hand, mothers were asked whether their deceased infants had dysentery in the 7days prior to their deaths during the verbal autopsies. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between dysentery and onset of bleeding at each sequential age for both cohorts of surviving (Table 9.12A) and deceased (Table 9.12B) infants separately. For assessing the independent effect of dysentery on bleeding symptoms, the odds ratios of dysentery were adjusted by logistic regression for gender, maturity, number of siblings, colostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed delivery and religion.

For cohort of surviving infants, the adjusted odds of umbilical bleeding if babies had dysentery in the last 3 months relative to if babies did not have dysentery was 1.49 (95% CI 1.12-2.01) at 2 days to 7 days of age, reflecting a 49% higher risk of umbilical bleeding being significantly associated with dysentery in the past last 3 months. Similar analysis with umbilical bleeding for 8 days to 3 months of age showed, dysentery in last 3 months was significantly associated with 47% higher risk of umbilical bleeding (adjusted OR= 1.47, 95% CI 1.05- 2.04) among surviving infants (Table 9.12A).

The adjusted odds of fresh intestinal bleeding for babies if had dysentery in last 3 months versus if did not have dysentery was 38.76 (95% CI 17.21-87.26) at 2 day to 7 days of age, indicating a 38.76 times significant higher risk of fresh intestinal bleeding associated with dysentery in last 3 months. Similar analysis with fresh intestinal bleeding for 8 days to 3 months and 3 months to 6 months of age showed, dysentery in last 3 months was significantly associated with 10.48 times (adjusted OR= 10.48, 95% CI 7.36-14.92) and 695.85 times (adjusted OR= 695.85, 95% CI 399.75-1211.27) higher risks for surviving infants, respectively.

For combination of bleeding symptoms, the adjusted odds of either nasal bleeding or bulging fontanel if babies had dysentery in last 3 months relative to if babies not having dysentery was 1.98 (95% CI 1.38-2.85) at 3 months to 6 months of age, reflecting a 98% higher risk of either nasal bleeding or bulging fontanel significantly associated with dysentery in last 3 months for surviving infants (Table 9.12A). Similar association found for nasal bleeding, bruising or umbilical bleeding at 2 day to 7 days (adjusted OR=1.54, 95% CI 1.15-2.01) at 2 days to 7 days of age and for 8 days to 3 months (adjusted OR= 1.50, 95% CI 1.10-2.04) with dysentery for surviving infants.

The adjusted odds of any bleeding for babies if having dysentery in last 3 months relative to if they did not have dysentery was 1.58 (95% CI 1.20-2.08) at 2 days to 7 days of age, indicating a 58% higher risk of any bleeding significant associated with dysentery in last 3 months. Similar analysis with any bleeding for 8 days to 3 months of age showed, dysentery was significantly associated with 2.49 times higher risk of any bleeding (adjusted OR=2.49, 95% CI 2.01-3.09).

Table 9.12A: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to dysentery in last 3 months among surviving infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Dysentery																								
1st day																								
No	24425	2					24411	16					24319	108	1				24424	3	1			
Yes	1992	0					1992	0					1978	14	1.59	0.84-2.79	1.50	0.84-2.69	1986	6	24.59	5.25-152.05	29.71	7.13-123.79
2-7 days																								
No	24420	7	1				24419	8					24013	414	1				24418	9	1			
Yes	1990	2	3.51	0.36-18.43	3.46	0.70-17.09	1992	0					1938	54	1.62	1.19-2.16	1.49	1.12-2.01	1966	26	35.88	16.26-87.11	38.76	17.2[illegible]-87.26
8-3 mo																								
No	24410	17	1				24396	31	1				24104	323	1				24357	70	1			
Yes	1990	2	1.44	0.16-6.09	1.24	0.28-5.49	1986	6	2.38	0.81-5.79	1.91	0.78-4.69	1949	43	1.65	1.16-2.28	1.47	1.05-2.04	1927	65	11.74	8.26-16.74	10.48	7.3[illegible]-14.92
2-6 mo																								
No	24371	56	1				24370	57	1				24421	6					24414	13	1			
Yes	1986	6	1.31	0.46-3.05	1.08	0.43-2.72	1987	5	1.08	0.34-2.66	1.12	0.44-2.81	1992	0					1435	557	728.95	421.10-1380.26	695.85	3[illegible].75-1281-27

Dysentery	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical Bleeding						Any Bleeding					
1st day																								
No	24409	18					24387	40	1				24304	123	1				24267	160	1			
Yes	1992	0					1989	3	0.92	0.18-2.89	0.90	0.28-2.94	1978	14	1.39	0.74-2.44	1.35	0.76-2.42	1975	17	1.31	0.74-2.16	1.26	0.75-2.12
2-7 days																								
No	24412	15	1				24398	29	1				24004	423	1				23966	461	1			
Yes	1990	2	1.64	0.18-7.04	1.64	0.37-7.27	1988	4	1.69	0.43-4.83	1.52	0.53-4.39	1936	56	1.64	1.21-2.18	1.54	1.15-2.01	1929	63	1.70	1.28-2.22	1.58	1.20-2.08
8-3 mo																								
No	24379	48	1				24341	86	1				24060	367	1				23914	513	1			
Yes	1984	8	2.05	0.84-4.37	1.67	0.78-3.59	1982	10	1.43	0.66-2.76	1.17	0.60-2.28	1942	50	1.69	1.23-2.28	1.47	1.09-2.02	1880	112	2.78	2.23-3.43	2.49	2.01-3.09
3-6 mo																								
No	24314	113	1				24222	205	1				24308	119	1				24045	382	1			
Yes	1981	11	1.19	0.58-2.22	1.09	0.57-2.11	1954	38	2.30	1.58-3.27	1.98	1.38-2.85	1981	11	1.13	0.55-2.11	1.13	0.61-2.12	1402	590	26.49	22.98-30.53	24.87	2153-28.73

* adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

Table 9.12B: Crude and adjusted* odds ratios with 95% CI for bleeding symptoms related to dysentery in 7 days of deaths among deceased infants

	Nasal Bleeding						Bruising						Umbilical Bleeding						*Fresh Intestinal Bleeding*					
	Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted		Bleeding status		Crude		Adjusted	
	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI	No	Yes	OR	95%CI	OR	95%CI
Dysentery																								
1st day																								
No	1681	7	1				1681	7	1				1661	27					1688	0				
Yes	56	2	8.56	0.85-46.33	10.62	1.74-64.75	57	1	4.21	0.09-33.63	4.69	0.48-45.73	58	0					56	2				
2-7 days																								
No	1639	49	1				1673	15	1				1609	79	1				1687	1	1			
Yes	57	1	0.59	0.01-3.56	1.33	0.17-10.39	57	1	1.96	0.05-13.15	2.74	0.33-22.82	57	1	0.36	0.01-2.13	0.48	0.06-3.59	49	9	309.86	40.85-13584.25	178.02	19.24-16[illegible]7.39
8-3 mo																								
No	1652	36	1				1675	13					1659	29	1				1672	16	1			
Yes	57	1	0.81	0.02-4.97	1.28	0.16-10.06	58	0					56	2	2.04	0.23-8.42	2.53	0.56-11.44	46	12	27.26	11.01-65.06	126.39	17.42-9[illegible].02
3-6 mo																								
No	1685	3					1686	2					1688	0					1686	2	1			
Yes	58	0					58	0					58	0					52	6	97.27	16.66-993.64		

Dysentery	Nasal Bleeding / Bruising						Nasal Bleeding / Bulging Fontanel						Nasal Bleeding / Bruising / Umbilical Bleeding						Any Bleeding					
1st day																								
No	1674	14	1				1672	16	1				1651	37	1				1645	43	1			
Yes	56	2	4.27	0.46-19.27	8.78	1.28-60.41	56	2	3.73	0.41-16.47	5.17	0.97-27.54	56	2	1.59	0.18-6.45	2.04	0.41-10.02	56	2	1.37	0.16-5.48	1.85	0.39-8[illegible].9
2-7 days																								
No	1626	62	1				1621	67	1				1556	132	1				1524	164	1			
Yes	56	2	0.94	0.11-3.69	2.08	0.46-9.37	54	4	1.79	0.46-5.08	1.78	0.40-7.90	55	3	0.64	0.13-2.02	0.79	0.19-3.41	48	10	1.94	0.86-3.97	1.88	0.76-4.63
8-3 mo																								
No	1640	48	1				1626	62	1				1615	73	1				1562	126	1			
Yes	57	1	0.59	0.01-3.64	0.85	0.11-6.54	57	1	0.46	0.01-2.77	0.65	0.09-4.91	55	3	1.21	0.24-3.86	1.67	0.49-5.66	45	13	3.58	1.72-6.97	4.73	2.34-9.55
3-6 mo																								
No	1684	4					1678	10					1684	4	1				1674	14	1			
Yes	58	0					58	0					58	0					51	7	16.41	5.34-45.48	14.71	4.97-43.47

* adjusted for gender, maturity at birth, number of siblings, clostrum feeding, exclusive breastfeeding, other morbidities, maternal age, maternal parity, obstructed labor and religion

Similar analysis with any bleeding for 3 months to 6 months of age showed, dysentery in last 3 months was found to be significantly associated with 24.87 times higher risk of any bleeding (adjusted OR= 24.87, 95% CI 21.52-28.73) for surviving infants. Similar pattern exited for any bleeding for 8 days to 3 months 178.02 (95% CI 19.24-1647.39) and for 3 months to 6 months (adjusted OR= 126.39, 95% CI 17.42-917.02) for surviving infants.

The adjusted odds of either nasal bleeding or bruising for babies if having dysentery in 7 days of deaths relative to if they did not have dysentery was 8.78 (95% CI 1.28-60.41) in the first day of life, reflecting a 8.78 times higher risk of any nasal bleeding or bruising being significantly associated with dysentery (Table 9.12B) in 7 days of deaths of deceased infants. The adjusted odds of any bleeding if babies had dysentery in 7 days of deaths relative to if they did not have dysentery was 4.73 (95% CI 2.34-9.55) at 8 days to 3 months of age, reflecting 4.73 times higher risk of any bleeding significantly associated with dysentery in 7 days of deaths. Similar analysis with any bleeding for 3 months 6 months of age showed, dysentery in 7 days of deaths was significantly associated with 14.71 times higher risk of any bleeding (adjusted OR= 14.71, 95% CI 4.97- 43.47) for deceased infants.

9.13 Summary Findings of Chapter 9

In this chapter analyses were conducted to determine possible associations between different predictors and risk of individual and combined bleeding symptoms. Crude and adjusted odd ratios with 95% CI were calculated to assess the association between different predictors and onset of bleeding at each sequential age (<24hours, 2days to 7 days, 8 days to 3 months and 3 months to 6 months) for both cohorts of surviving and deceased infants. Estimates of risks were adjusted for potential confounders.

When analyzed, the association between gender and bleeding status of infants, was found that male infants were significantly associated with increased risk of bleeding at 8 days to 3 months of age in the cohort of surviving infants and non-significantly associated with increased risk up to 3 months of age for the cohort of deceased infants.

To look at the effect of gestational age on infantile bleeding, premature babies were defined as born at gestational at age < 37 weeks and mature babies as born at gestational age >=37 weeks. It was found that prematurity was significantly associated with increased risk of bleeding in the first day of life for surviving cohort and for first 7 days of life for cohort of deceased infants. In the analysis, twins were found to be significantly associated with increased risk of bleeding at 3 months to 6 months of age among surviving cohort and no such significant association was found in the cohort of deceased infants. Low birth weight was defined as <2.5 kg and normal birth weights as >=2.5 kg. Low birth weights were found to be significantly associated with reduction of risk of bleeding at 2 days to 7 days of age among cohort of surviving infants.

Breathing difficulties in the 7 days of deaths were found to be significantly associated with increased risk of bleeding in the first day of life for the cohort of deceased infants.

Diarrhoea in the last 3 months was found to be significantly associated with increased risk of bleeding from 2 days to 6 months of age for cohort of surviving infants. Diarrhoea within 7 days of death was found to be significantly associated with increased risk of bleeding for 3 months to 6 months of age for the cohort of deceased infants. Dysentery in last 3 months was found to be significantly associated with increased risk of bleeding up to 6 months of age for the surviving cohort. Dysentery within 7 days of death was found to be significantly associated with increased risk of bleeding for 8 days to 6 months of age for cohort of deceased infants.

Chapter 10. Maternal PIVKA-II Analysis

In this chapter, association between bleeding status of infants and maternal PIVKA-II levels in the 3rd trimester of pregnancy and 3 months post partum have been analyzed. PIVKA-II is a plasma protein and is released in absence of vitamin K and stands for "Protein Induced in Vitamin K Absence". Higher levels of PIVKA-II reflect lower levels of vitamin K. The commonly reported cut-off for PIVKA-II for adult female is 2 ng/ml[34]. In this analysis it was assumed that maternal 3rd trimester PIVKA-II levels would correspond to infants' vitamin K levels at birth and maternal 3-month post partum PIVKA-II levels would correspond to how much vitamin K infants got through lactation. It was assumed that maternal plasma PIVKA-II concentration could be a proxy measure of infants' vitamin K status, and thus, could link to risk of infantile bleeding due to vitamin K deficiency. Based on this assumption the analysis was done to evaluate the relationship in the context of the JiVitA sub-study design.

Maternal blood samples were collected at 3rd trimester of pregnancy and 3 months post partum visits to estimate maternal PIVKA-II levels. Samples were taken from the sub-study plasma specimens archives of mothers whose infants had bleeding symptoms within their 6 months of age. Using a 1:2 sampling ratio, for each sample of a mother whose infant had bleeding, two matched mothers' samples whose infants did not have bleeding were drawn form the sample archives. Matching was done on gestational age at birth for infants.

Maternal 3rd trimester plasma PIVKA-II levels were measured for 295 mothers. The 3rd trimester PIVKA-II values for two mothers were found to be very extreme and were excluded from the analysis. Among the rest 293 mothers, 103 were mothers of infants who had bleeding and 190 were mothers of infants who did not have bleeding. Similarly, maternal plasma PIVKA-II levels at 3-month post partum were measured for 295 mothers. Among these 295 mothers, 104 were mothers of infants who had any bleeding and 191 were mothers of infants who did not have bleeding. In total, laboratory analyses of 3rd trimester and 3-month postpartum PIVKA-II levels were measured for 295 mothers (1.01%), among them 272 were mothers of surviving infants (1.03%) and rest 23 were mothers of deceased infants (0.83%).

As the number of individual bleeding symptoms was very small for different age of onset intervals for which PIVKA-II samples were drawn, it was not possible to evaluate the plasma protein concentration differences by individual bleeding symptoms but it was possible to evaluate differences for any bleeding symptoms.

For the same reason there was insufficient power to analyze PIVKA-II levels separately across cohorts of surviving and deceased infants. Maternal plasma protein concentrations were also assessed by their dietary intake during the 3rd trimester of pregnancy and at 3 months postpartum periods, specifically their reported frequencies of intake of dark green leafy vegetables (DGLV). Dietary intakes were also evaluated in this sub sample of mothers to look for any association between their DGLV consumption and their infants' bleeding, irrespective of maternal plasma PIVKA-II levels.

10.1 Maternal 3rd Trimester Mean PIVKA-II Levels and Bleeding Status of Infants

When the means of maternal 3rd trimester PIVKA-II levels among the infants who had and who did not have bleeding were compared based on the age of onset of bleeding, it was found that the mean maternal PIVKA-II levels for infants who had bleeding was 1.89 ng/ml (SD ± 0.96) for <24 hours onset, 1.87 ng/ml (SD ± 1.02) for 2-7 days of onset, 1.91 ng/ml (SD ± 1.91) for 8 days to 3 months onset, and 2.12 ng/ml (SD ± 0.62) for 3 months to 6 months of onset of age (Table 10.1). Corresponding means of maternal PIVKA-II levels for all mothers of infants who did not have bleeding was 2.05 ng/ml (SD ± 0.79) in the 3rd trimester of pregnancy. Maternal plasma PIVKA-II levels were not statistically different among the groups of infants who had and did not have bleeding.

Table 10.1: Comparison between mean maternal 3rd trimester PIVKA-II levels and their infants' bleeding status

	Infants who had bleeding	**Infants who did not have bleeding**	
3rd Trimester PIVKA II (in ng/ml)			**p-Value**
<24 hours	**n=8**	**n=190**	
Mean (±SD)	1.89(0.96)	2.05 (0.79)	0.5849
2-7 days	**n=31**	**n=190**	
Mean (±SD)	1.87 (1.02)	2.05 (0.79)	0.2616
8d -3 mo	**n=30**	**n=190**	
Mean (±SD)	1.91(0.73)	2.05 (0.79)	0.3582
3-6mo	**n=31**	**n=190**	
Mean (±SD)	2.12 (0.62)	2.05 (0.79)	0.6459
At Any Age Interval	**n=103**	**n=190**	
Mean (±SD)	1.97 (0.81)	2.05 (0.79)	0.4084

10.2 Maternal 3-month post partum Mean PIVKA-II Levels and Bleeding Status of Infants

When analyzed maternal 3-month post partum plasma PIVKA-II levels with bleeding status of infants, it was found that the means were 1.91 ng/ml (SD ± 0.34) for <24 hours onset, 2.03 ng/ml (SD ± 0.62) for 2-7 days onset , 2.03 ng/ml (SD ± 0.61) for 8 days to 3 months onset, and 2.10 ng/ml (SD ± 0.53) for 3 months to 6 months of age onset for infants who had bleeding problems. The corresponding overall mean maternal PIVKA-II level at 3 months postpartum was 1.98 ng/ml (SD ± 0.55), which did not differ statistically between groups infants who had and did not have bleeding (Table 10.2).

Table 10.2: Comparison between mean maternal 3-month post partum PIVKA-II levels and their infants' bleeding status

3-month post partum PIVKA II (in ng/ml)	**Infants who had bleeding**	**Infants who did not have bleeding**	p-Value
<24 hours	**n=8**	**n=191**	
Mean (±SD)	1.91(0.34)	1.98 (0.55)	0.7477
2-7 days	**n=31**	**n=191**	
Mean (±SD)	2.03 (0.62)	1.98 (0.55)	0.6629
8d-3mo	**n=31**	**n=191**	
Mean(±SD)	2.03 (0.61)	1.98 (0.55)	0.6423
3-6 mo	**n=31**	**n=191**	
Mean (±SD)	2.10 (0.53)	1.98 (0.55)	0.2607
At Any Age Interval	**n=104**	**n=191**	
Mean (±SD)	2.04 (0.57)	1.98 (0.55)	0.3382

10.3 Maternal 3rd Trimester PIVKA-II Levels and Bleeding Status of Infants

When bleeding status of infants were analyzed by maternal 3rd trimester PIVKA-II level, for 25% infants who had early bleeding compared to 44.2% of the infants who did not have bleeding had their maternal PIVKA-II level more than 2ng/ml, but the difference was not statistically significant (p=0.283). For bleeding symptoms occurring between 2-7 days, for about 26% infants who had bleeding had maternal PIVKA-II level above the cut off compared to 44.2% of infants did not have bleeding, the difference was statistically significant (p=0.054).

Table 10.3: Distribution of bleeding status of infants by their maternal 3rd trimester PIVKA-II levels

Time of onset	**Infants who had bleeding**		**Infants who did not have bleeding**		
<24 hours					
PIVKA-II level	**n=8**	**%**	**n=190**	**%**	
≤2ng/ml	6	75.0	106	55.8	
>2ng/ml	2	25.0	84	44.2	0.283
2-7 days					
PIVKA level	**n=31**	**%**	**n=190**	**%**	
≤2ng/ml	23	74.2	106	55.8	
>2ng/ml	8	25.8	84	44.2	0.054
8days-3months					
PIVKA-II level	**n=30**	**%**	**n=190**	**%**	
≤2ng/ml	19	63.3	106	55.8	
>2ng/ml	11	36.7	84	44.2	0.438
3mon-6months					
PIVKA-II level	**n=31**	**%**	**n=190**	**%**	
≤2ng/ml	15	48.4	106	55.8	
>2ng/ml	16	51.6	84	44.2	0.443

When compared for bleeding symptoms occurred between 8days to 3 months of age, similarly for 36.7% of infants who had bleeding and 44.2% infants who did not have bleeding had maternal PIVKA-II level above cut off (p=0.438). Higher percentage of infants who had bleeding (51.6%) compared to infants who did not have bleeding were found to have maternal PIVKA-II above the cut off level, although this difference was not statistically significant (p=0.443)

10.4 Maternal 3-month post partum PIVKA-II Levels and Bleeding Status of Infants

When bleeding status of infants were analyzed by maternal 3-month post partum PIVKA-II level(Table 10.4), for 37.5% of infants who had early bleeding compared to 43.5% of the infants who did not have bleeding had maternal PIVKA-II level above the cut off, but the difference was not statistically significant (p=0.739). Similar distribution (41.9% and 43.5%) were found for bleeding symptoms occurring between 2-7 days of age for maternal PIVKA-II level above 2ng/ml for infants who had and did not have bleeding, respectively.

When compared for bleeding symptoms occurring between 8 days to 3 months of age, for 35.5% of infants who had bleeding and 43.5% infants who did not have bleeding had PIVKA-II level above cut off, the difference was not statistically significant (p=0.405). Higher percentage of infants who had bleeding (54.8%) compared to infants who did not have bleeding (43.5%) were found to had maternal PIVKA-II levels above the cut off level, although the difference was not statistically significant (p=0.237).

Table 10.4: Distribution of bleeding status of infants by their maternal 3 month postpartum PIVKA-II levels

Time of onset	Infants who had bleeding		Infants who did not have bleeding		
<24 hours					
PIVKA-II level	**n=8**	**%**	**n=191**	**%**	
≤2ng/ml	5	62.5	108	56.5	
>2ng/ml	3	37.5	83	43.5	0.739
2-7 days					
PIVKA-II level	**n=31**	**%**	**n=191**	**%**	
≤2ng/ml	18	58.1	108	56.5	
>2ng/ml	13	41.9	83	43.5	0.874
8 days-3 months					
PIVKA-II level	**n=31**	%	**n=191**	**%**	
≤2ng/ml	20	64.5	108	56.5	
>2ng/ml	11	35.5	83	43.5	0.405
3 mon-6 months					
PIVKA-II level	**n=31**	**%**	**n=191**	**%**	
≤2ng/ml	14	45.2	108	56.5	
>2ng/ml	17	54.8	83	43.5	0.237

10.5 Maternal DGLV Consumption during 3rd Trimester of Pregnancy and Bleeding Status of Infants

This following section addressed the relationship between maternal dietary intake of dark green leafy vegetables during pregnancy and post partum period and risk of infant bleeding. Similar analysis was also conducted with maternal plasma PIVKA-II concentrations for these dietary variables. At the 3rd trimester of pregnancy mothers were asked, how many times in the last seven days they ate DGLV.

Table 10.5: Distribution of bleeding status of infants by their maternal DGLV consumption during 3rd trimester of pregnancy

Maternal 3rd Trimester DGLV Consumption (times in 7 days)	**Infants who had bleeding** n=1096		**Infants who did not have bleeding** n=11268	
	No.	%	No.	%
None	383	34.9	3953	35.1
Once	269	24.5	2705	24.0
Twice	217	19.8	2287	20.3
Thrice	93	8.5	967	8.6
4+	127	11.6	1237	10.9
Don't know	7	0.6	119	1.1
Pearson $Chi^2(5)$ =2.3022			*P-value: 0.806*	
Mean (in times)	1.56		1.56	
Median (in times)	1.0		1.0	
SD±	1.93		1.99	
Ranksum test Z= -0.163			*P-value: 0.870*	

This analysis was intended to see whether bleeding status of infants differed by maternal DGLV consumption (which could be a remote proxy for vitamin K level of infants). Over one third of the mothers of both types of infants did not eat any dark green leafy vegetables (DGLV) during the last seven days of interviews (Table 10.5).

Bleeding status of infants did not vary on the variation of maternal consumption of dark green leafy vegetables for the rest of the categories. The mean and median times of consumptions of DGLV were exactly the same for mothers of both types infants who had bleeding and who did not have bleeding.

10.6 Maternal PIVKA-II Levels and DGLV Consumption during 3rd Trimester of Pregnancy

When the association between maternal PIVKA-II levels and DGLV consumption during 3rd trimester of pregnancy were analyzed, it was found that among the mothers who ate DGLV in last seven days, 71.4% had PIVKA-II levels more than 2 ng/ml and 65.1% had PIVKA-II levels less than 2ng/ml (Table 10.6), the difference was not statistically significant (p=0.299). The median times of DGLV consumption was 2 days in last 7 days (SD ± 1.48) for maternal PIVKA-II level more than 2ng/ml and 1 day in last 7 days (SD ± 1.97) for maternal level less than 2ng/ml, the difference was not statistically significant (p=0.3003).

Table 10.6: Association between maternal PIVKA-II levels and DGLV consumption during 3rd trimester of pregnancy

	PIVKA-II >2ng/ml		***PIVKA-II ≤2ng/ml***	
Maternal DGLV Consumption in last 7 days	**n=98**	**%**	**n=152**	**%**
No	28	28.6	53	34.9
Yes	70	71.4	99	65.1
Pearson Chi²(1) 1.0787				*P-value=0.299*
Mean	1.64		1.66	
Median	2		1	
SD±	1.48		1.97	
Ranksum test z =-1.036				*P-value: 0.3003*

10.7 Maternal DGLV Consumption during 3-month post partum and Bleeding Status of Infants

Similar to 3rd trimester of pregnancy at the 3 months post partum interviews mothers were asked about the frequency of dark green leafy vegetables they consumed in the last seven days of interviews (Table 10.7). Analysis was done to see whether maternal DGLV consumption during lactation affected bleeding status of infants. Over one third of the mothers of both types of infants reported that they did not consume any dark green leafy vegetables (DGLV) during the last seven days of their 3-month post partum interviews. Similar to 3rd trimester consumption, bleeding status of infants did not vary with consumption of dark green leafy vegetables during last seven days of interview at 3 months post partum visits. The mean and median times of maternal DGLV consumption during 3 months post partum were exactly the same for both types of infants (Table 10.7).

Table 10.7: Distribution of bleeding status of infants by their maternal DGLV consumption during 3-month post partum period

Maternal 3 Months Post Partum DGLV Consumption (times in 7days)	**Infants who had bleeding** n=2518		**Infants who did not have bleeding** n=23820	
	No	%	No	%
None	862	34.2	8308	34.9
Once	620	24.6	5819	24.4
Twice	489	19.4	4542	19.1
Thrice	238	9.5	2258	9.5
4+	289	11.5	2750	11.5
Don't know	20	0.8	143	0.6
Pearson $Chi^2(5)= 1.8496$			*P-value: 0.870*	
Mean (in times)	1.59		1.59	
Median (in times)	1.0		1.0	
SD±	1.92		2.0	
Ranksum test Z=-0.409			*P-value: 0.6826*	

10.8 Maternal PIVKA-II Levels and DGLV Consumption during 3 Month Post Partum

When the association between maternal PIVKA-II levels and DGLV consumption in the last 7 days of interview for 3-month post partum visits were analyzed, it was found that among the mothers who ate DGLV in last seven days 67.2% had PIVKA-II levels more than 2 ng/ml and a very similar 67.5% had PIVKA-II levels less than 2 ng/ml, the difference was not statistically significant (p=0.959). The median time of DGLV consumption for both PIVKA-II levels were 1 day in last 7 days.

Table 10.8: Association between maternal PIVKA-II levels and DGLV consumption during 3-month post partum

	PIVKA-II >2ng/ml		***PIVKA-II ≤2ng/ml***	
Maternal DGLV Consumption in last 7 days	**n=125**	**%**	**n=163**	**%**
No	41	32.8	53	32.5
Yes	84	67.2	110	67.5
Pearson $Chi^2(1)$ 0.0026			*P-value=0.959*	
Mean	1.50		1.61	
Median	1		1	
SD±	1.67		1.94	
Ranksum test z=-0.325			*P-value: 0.7455*	

10.9 Summary Findings of Chapter 10

In this chapter, associations between bleeding status of infants and maternal PIVKA-II levels in the 3rd trimester of pregnancy and 3 months post partum have been reported. When the means of maternal 3rd trimester PIVKA-II levels among the infants who had bleeding and who did not have bleeding were compared based on age of onset of bleeding for different combination of bleeding symptoms, it was found that the mean maternal PIVKA-II levels for infants who had bleeding were similar (ranges 1.87-2.12ng/ml) to the corresponding means of maternal PIVKA-II levels for the mothers of infants who did not have bleeding in the 3rd trimester of pregnancy (2.05 ng/ml, SD ± 0.79).

Similarly, maternal 3-month post partum PIVKA-II also did not differ among the infants who had bleeding and who did not have bleeding. When the distribution of bleeding status of infants were examined with maternal 3rd trimester PIVKA-II level, for about 26% infants who had bleeding had maternal PIVKA-II level above 2ng/ml compared to 44.2% of infants who did not have bleeding at 2-7 days age of onset, the difference was statistically significant (p=0.054). For rest of the distribution of maternal PIVKA-II levels bleeding status of infants did not differ statistically.

In this chapter, the association between bleeding status of infants and maternal DGLV consumption during 3rd trimester of pregnancy and 3 months post partum were also explored. Over one third of the mothers of both types of infants did not eat any dark green leafy vegetables (DGLV) during the last seven days of both periods.

Bleeding status of infants did not vary with maternal consumption of dark green leafy vegetables during last seven days of interviews for both 3rd trimester of pregnancy and 3 month post partum.

When the association between maternal PIVKA-II levels and DGLV consumption during 3rd trimester of pregnancy and 3-month post partum were analyzed, it was found that there was no association between maternal PIVKA-II levels and DGLV consumption for both time periods.

Chapter 11. Discussion

11.1 Discussion

Data on vital statistics were available for 29,844 live born infants at the outset for this study. The number of infants who survived up to 6 months of age was 26,705, which represented the full cohort of the surviving infants (89.5%) in this analysis. The total number of infants who died in the first six months of life was 3139, which represented the full analytical cohort of infants who died by six months of age (10.5%). A total of 1941 infants died within 7 days of birth, representing an early neonatal mortality rate of 65 per 1000 live births. The reporting of neonatal mortality in this study was found to be similar to the reporting of 62 in 1000 live births in Sylhet district in 2003[71].

For the cohort of surviving infants, questions on nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding (red blood in stool), dark stools, excessive bleeding during circumcision and bulging fontanel were asked during the 6 months follow up visits. Parents were asked to report the listed bleeding symptoms with the time of onset for first episodes. For the cohort of deceased infants, parents were asked for the same list of bleeding symptoms along with the time of onset of the first episodes during the deceased infants' verbal autopsies. Verbal autopsies were scheduled one week after deaths of infants. Most of the verbal autopsies were completed within 3-4 weeks of the schedule. Any bleeding symptom was constructed considering parental reporting of all bleeding symptoms that their infants had for both the cohorts. Bleeding symptoms were categorized based on the time of onset of bleeding as early onset (< 24 hours), classical onset (2 days to 7 days) and late onset (8 days to 6 months)[3].

Data were analyzed based on the time of onset of bleeding for individual and combined bleeding symptoms with other explanatory variables e.g. breastfeeding, infantile characteristics, parental characteristics, infants' morbidities etc. separately for surviving and deceased infants as a means to assess the consistency in association and controlling for potential biases and confounders. Symptoms were combined to evaluate the potential that they could confer different levels of risk for mortality of infants.

Among 26,705 infants who survived up to 6 months of age, 2395 (9.0%) were reported by parents to have had at least one bleeding symptom up to that age. In contrast, among 3139 infants who died by 6 months of age (the deceased cohort), 650 (20.7%) were reported to have had bleeding symptoms prior to death, reflecting a frequency that was 2.3 times greater than surviving infants. Thus, of all 29,844 infants in the study, including both survivors and infants who later died by age six months, parents reported symptoms of bleeding in 3045 or 10.2% of all study infants.

Higher proportions of infants who died in the first six months had early and classic onset of bleeding symptoms than the surviving infants (38.8% vs. 7.4% and 33.9% vs. 21.9%, respectively), reflecting both the possibility that early occurrence of bleeding was more likely to be fatal than later bleeding, but also the fact that fewer infants in the deceased cohort survived compared to the older ages. Among surviving infants, 66.7% reported as initial or only episode of bleeding beyond the first week of life. Overall, higher percentages of deceased infants had nasal bleeding (31.5% vs. 4%), bruising (14.8% vs. 5.3%) and bulging fontanel (17.1% vs. 14.5%) than surviving infants.

This study finding appeared to be much higher compared to findings in studies conducted in Thailand and Malaysia. The Thai study reported incidence rates of classical VKDB as 0.9 per 1000 life births[8] and the Malaysian study reported incidence rates of classical VKDB as low as 0.3 per1000 live births[9]. The incidence of late onset (8 days to 6 months) of any bleeding was 59.8 among surviving infants and 133.6 among deceased infants per 1000 infants, which was found to be much higher than 32 per 1000 live births reported in urban China[5]. A study conducted in Vietnam reported incidence of late VKDB as 1.4 per 1000 live births in the rural area[12]. In Japan the incidence of late VKDB was reported to be around 0.2 per 1000 live births[1]. The incidence rates of late VKDB in infants with no history of Vitamin K prophylaxis varied from 0.04 to 0.7 per 1000 births in other Asian and European studies[21].

The incidence rates of nasal bleeding were 3.6 and 65.3 per 1000 infants among surviving and deceased infants, respectively. Nasal bleeding occurring in the first day of life occurred virtually only in infants who died, with the relative risks being 344.6 (95% CI 92.3-2893.4), 125.8 (95%CI 62.9-284.8) and 11.1 (95% CI 7.3-16.3) during the early, classic and late periods, respectively.

The overall incidence rates of bruising were 4.8 and 30.6 per 1000 infants among surviving and deceased infants respectively, revealing a 6.4 (95% CI 4.9-8.5) times greater risk in the cohort of infants who died by six months of age. Bleeding at the site of the umbilicus was more commonly reported in both cohorts of infants, with overall incidence rates of 36.6 (surviving cohort) and 72.3 (deceased cohort) per 1000 infants.

The incidence rate of bulging fontanel was 13.0 and 35.4 per 1000 infants among the cohort of surviving and deceased infants, respectively. The relative risk was 2.7 (95% CI 2.2-3.4) times greater in cohort of infants who died by 6 months of age than surviving infants. Relative risks were higher for early (8.3, 95% CI 5.2-13.2) and classic onset (14.9, 95% CI 8.2-27.2), reflecting a higher risk of bulging fontanel occurring during first week of life among the cohort of deceased infants.

This study found very high case fatality rates for early onset nasal bleeding (97.6%, 95% CI 94.3-99.8) and classic onset nasal bleeding (90.1%, 95% CI 83.9-96.3). High case fatality rates were also found to be associated with early onset (79.5%, 95% CI 70.5-88.5) bruising and classic onset (66.7%, 95% CI 47.4-85.9) bruising. Case fatality rates were also very high for any nasal bleeding or bruising (88% and 85%) and any nasal bleeding or bulging fontanel (72.4% and 75.9%) for the early and classical onset, respectively. Reported case fatality rate for any bleeding was found to be 21.3% (95% CI 19.8-22.8) in this study.

Bulging fontanel during infancy could be a manifestation of intracranial bleeding[12], although it is more often understood to represent changes in intracranial blood flow volume[72]. In this study bulging fontanel was considered as a proxy to measure intracranial bleeding. The case fatality rate of bulging fontanel was found to be 24.2% (95% CI 22.2-26.2) in this study, which was very similar to 24% case fatality reported in another study in Thailand[8].

Given the importance of exclusive breastfeeding (EBF) in the literature as a potential causal determinant of bleeding related to vitamin K deficiency in early life [3-5,10,11,23,42], the infantile bleeding status were analyzed by patterns of breastfeeding in both the cohorts of surviving and deceased infants.

When looking at the EBF rates among the surviving infants, 42.7% were exclusive breastfed in the first day of life, 40% at 2 to 7 days of age, 29.7% at 8 days to 3 months of age and 16.7% at 3 months to 6months of age were found (Table 8.2). For the cohort of deceased infants, 20.8% were exclusively breastfed in the first day of life, 17.8% at 2 days to 7 days of age, 15.5% at 8 days to 3 months of age and 15.2% at 3 months to 6 months of age. Significantly higher percentage of infants who had bleeding (25.9%) were on exclusive breastfeeding than infants who did not have bleeding (17.2%) at 2 day 7 days age ($p=<0.001$) among the deceased infants (Table 8.4).

According to the literature exclusive breastfeeding reported to be significantly associated with increased risk of infantile bleeding [3, 4, 5, 10,11, 23, 42] as breastmilk contains low levels of vitamin K [65, 66] and the risk was reported to be 15-20 times higher than given other types of foods [11]. It was mentioned that intestinal floras of breastfed infants were not efficient in the synthesis of vitamin K, since lactobacilli do not synthesis vitamin K [21]. In addition to that it was also mentioned that exclusive breastfeeding result in intestinal floras that could be low in vitamin K producing bacteria[71].

In this study, exclusive breastfeeding appeared to be significantly associated with 39% higher risk of umbilical bleeding (adjusted OR= 1.39, 95% CI 1.11-1.73) at 8 days to 3 months of age compared to non-exclusive breastfeeding during that time period in the analyses among the surviving infants. Similarly, exclusive breastfeeding shown to be significantly associated with 37% higher risk (adjusted OR=1.37, 95% CI 1.11-1.68) of any nasal bleeding, bruising or umbilical bleeding at 8 days to 3 months of age among surviving infants.

For the cohort of the deceased infants exclusive breastfeeding was also found to be significantly associated with a 3.01 times higher risk of nasal bleeding at 2 to 7 days of age (adjusted= 3.01,95% 1.36-6.65). When similar analysis was conducted for combination of bleeding, EBF was found to be significantly associated at a 2.26 times higher risk of nasal bleeding or bulging fontanel (adjusted OR=2.26, 95% CI 1.18-4.33) at 2 to 7 days of life among the cohort of the deceased infants. These findings also support the existing findings of exclusive breastfeeding significantly associated with increased risk of bleeding[3,4,5,10,11,23,42].

According to literature, colostrum is rich in vitamin K[5, 59] and thus protective of vitamin K deficiency bleeding in early infancy. For the cohort of surviving infants the multivariate analyses with colostrum feeding and risk of bruising, umbilical bleeding and fresh intestinal bleeding in the first day of life reflected 13 to 59% reduction of risk of bleeding associated with colostrum feeding, although neither of the 95% CIs were statistically significant (Table 8.7).

For the cohort of deceased infants, colostrum feeding appeared to be non significantly associated with 8% reduction of umbilical bleeding in the 1st day of life (adjusted OR=0.92, 95% CI 0.21-4.10). Similarly, colostrum feeding was found to be non-significantly associated with an 11% risk reduction of nasal bleeding at 2 to 7 days of age (adjusted OR= 0.89, 95% CI 0.20-3.96) in the same group.

Although not statistically significant, the direction and magnitude of the association o these findings supports the protective effect of colostrum in preventing infantile bleeding in the early days of life reported by other findings[5,59]. When the association between gender and bleeding symptoms were analyzed, it was found that male infants were at a 48% significantly higher risk of fresh intestinal bleeding (red blood in stool) at 8 days to 3 months of age compared to their female counterparts (adjusted OR=1.48 ,95% CI 1.03-2.12) in the surviving cohort. This study finding of male infants being associated with increased risk of bleeding was in agreement with the earlier findings by Sutor AH *et al.*[3], Chuansumrit *et al.*[8], HE Zhang *et al.*[5] and Cesar G *et al.*[1].

In 2002, Zhou *et al.* reported a higher incidence of VKDB (22.52 per 1000 live births) in the preterm babies compared to the term babies (2.96 per 1000 live births)[10]. Other studies also reported similar associations of prematurity as a risk factor for infantile bleeding[23,42]. According to the current knowledge, premature babies may have an immature or underdeveloped gut and hepatobiliary system, which could predispose them to a low vitamin K deficiency status[2,18].

To look at the effect of gestational age on infantile bleeding, in this study the premature babies were defined as babies born at gestational age <37 weeks and mature babies as born at gestational age >=37 weeks. For the cohort of surviving infants, prematurity was found to be significantly associated with 4.15 times higher risk of bruising in the first day of life (adjusted OR=4.15, 95% CI 1.49-11.53).

Similarly, for the cohort of deceased infants, prematurity was found to be significantly associated with a 94% increased risk of umbilical bleeding at 2 to 7 days of age (adjusted OR=1.94, 95% CI 1.12-3.36). These findings of prematurity being significantly associated with increased risk of bleeding also supported the association of prematurity as a risk of bleeding during infancy as found in other studies[10, 23, 42].

When the association between number of siblings at birth and fresh intestinal bleeding symptoms were measured, twins appeared to have a 4.7 times increased risk of fresh intestinal bleeding (adjusted OR=4.66, 95% CI 2.03-10.68) than singleton babies at 3 months to 6 months of age in the cohort of surviving infants. The increased risk of bleeding associated with twins could be explained by the likelihood of prematurity among twins and less nutrition supply as they compete with other siblings at these early ages of life. According to one study, obstructed labor was reported as a risk factor for VKDB as bleeding could occur in the brain because of trauma in the process of delivery[23]. The literature also suggests birth asphyxia as one of the risk factors of VKDB, as asphyxiated babies often have obstructed or prolonged labors[10,23]. Mothers were asked at the 3 months post partum interviews whether they had obstructed labor for the index babies.

When the association between obstructed labor and umbilical bleeding were analyzed, obstructed labor was found to be significantly associated with umbilical bleeding in the first day of life (adjusted OR=1.73, 95% CI 1.12-2.67) and for 8 days to 3 months of age (adjusted OR =1.41, 95% CI 1.07- 1.84) for the cohort of surviving infants.

When similar analysis was conducted for the cohort of deceased infants, obstructed delivery was found to be significantly associated with 13.4 times increased risk of nasal bleeding (adjusted OR= 13.40, 95% CI 3.04-59.13) and 4.2 times increased risk of either nasal bleeding or bulging fontanel (adjusted OR= 4.23 (95% CI 1.28-13.93) in the first day of life. Thus the multivariate analysis with obstructed labor and infantile bleeding in this study also supported the reported studies.

Studies suggested different risk of VKDB in different ethnic groups[11]. Analyses were also conducted to see the effect of religion on infantile bleeding. When analyzed, Islam appeared to be significantly associated with bruising (adjusted OR=4.91, 95% CI 1.52-15.86) and with any nasal bleeding or bruising (adjusted OR=4.17, 95% CI 1.32-13.13) in the first day of life. When the cohort of deceased infants were similarly analyzed for the combination of bleeding symptoms, being born in a Muslim family was significantly associated with 2.78 times increased risk of any nasal bleeding or bulging fontanel (adjusted OR= 2.78, 95% CI 1.16-6.59) in the first day of life. These differences in risks of bleeding could be explained by different early feeding practices as part of different cultural practices prevailing among Hindu families compared to Muslim families in the rural areas.

According to other research studies, morbidities e.g. illness in the two weeks of birth, diarrhoea etc. are significantly associated with an increased risk of bleeding during infancy[10,11,21,23]. In the data collected in this study, mothers were asked whether their surviving infants suffered from cough/cold, high fever, diarrhoea and dysentery in the last 3 months during the 6 months follow up visits.

On the other hand, mothers were asked during the verbal autopsies; whether their deceased infants suffered from cough/cold, cough with high fever, breathing difficulties, diarrhea and dysentery in the 7 days prior to death. In this study, reference time periods of morbidities were different for surviving and deceased infants. It would be better if same morbidity questions in relation to the time of onset of bleeding were asked in both groups of infants.

As the questions on bleeding were nested mid way of data collection of an ongoing trial, it was not possible to add detailed questions on morbidities to the existing questionnaire. So, the estimates of association between morbidities and bleeding symptoms could not be explained by temporal relationship for both surviving and deceased infants. But, if it is assumed that the pattern of morbidities would have been the same over the time periods of the infants who suffered morbidities during the data collection, then the morbidities can be considered as proxy of morbidities suffered by the infants during the bleeding episodes.

For the cohort of surviving infants, high fever in last 3 months appeared to be significantly associated with increased risk of fresh intestinal bleeding at 8 days to 3 months of age (adjusted OR= 1.55 (95% CI 1.02-2.26) and for 3 months to 6 months of age (adjusted OR= 1.30, 95% CI 1.03-1.64). Similar association was also found for fever and any nasal bleeding or bulging fontanel (adjusted OR=1.4, 95%CI 1.11-3.02) at 8 days to 3 months of age and (adjusted OR=2.19, 95% CI 1.59-3.00) for 3 months to 6 months of age. The increased risk of fresh intestinal bleeding for high fever could be explained by infective gastroenteritis accompanied by fever.

When the association between breathing difficulties within 7 days prior to death were analyzed with the bleeding symptoms for the cohort of deceased infants, it was found that a 4.93 times higher risk of umbilical bleeding (adjusted OR=4.93, 95% CI 1.55-15.69) and 3.86 times higher risk of any nasal bleeding, bruising or umbilical bleeding in the first day of life (adjusted OR= 3.86 (95% CI 1.44-10.36) were significantly associated with breathing difficulties.

These finding of breathing difficulties as a risk factor associated with bleeding in the first day of life is supported in other findings[10,23]. For the cohort of surviving infants, diarrhoea in the last 3 months were seen to be significantly associated with a 3.06 times higher risk of bruising at 8 days to 3 months of age (adjusted OR=3.06, 95% CI 1.53-6.12). Similarly, a 43% higher risk of umbilical bleeding at 2 to 7 days (adjusted OR= 1.43, 95% CI 1.15-1.79) and 57% higher risk of umbilical bleeding (adjusted OR= 1.57, 95% CI 1.23-2.00) for 8 days to 3 months of age were found to be associated with diarrhoea.

A similar pattern of increased risk was found to persist for any combination of bleeding from 2 days to 6 months of age for the cohort of surviving infants. When similar analysis was conducted for the cohort of deceased infants, diarrhoea within 7 days prior to deaths were found to be significantly associated with 14.19 times higher risk of nasal bleeding at 3 months to 6 months of age (adjusted OR=14.19 (95% CI 1.20-167.73) and 6.37 times higher risk of fresh intestinal bleeding at 3 months to 6 months of age (adjusted OR=6.37, 95% CI 1.01-40.25). During diarrhea, Vitamin K_2 producing gut flora could be washed out and predispose babies to low levels of vitamin K. These findings of diarrhoea was significantly associated with an increased risk of bleeding in other studies too[11,21,23]. For the cohort of surviving infants, dysentery in the last 3 months was found to be highly significantly associated with increased risk of fresh intestinal bleeding (red blood in stool) up to 6 months of age, at 2 to 7 days the adjusted OR was 38.76 (95% CI 17.21-87.26), for 8 days to 3 months the adjusted OR was 10.48 (95% CI 7.36-14.92) and for 3 months to 6 months the adjusted OR was 695.85 (95% CI 399.75-1211.27).

In the bi-variate analysis it was also found that a higher proportion of infants who had fresh intestinal bleeding (86.6%) compared to those who did not have fresh intestinal bleeding (5.1%) suffered from dysentery in the last 3 months and the difference was statistically significant (p= <0.001). This finding could be explained by the reported association of risk of dysentery with introduction of early complementary feeding among infants[67].

When similar analysis was conducted for the cohort of deceased infants, it was found that dysentery within 7 days prior to death was significantly associated with a very high risk of fresh intestinal bleeding for 8 days to 3 months (adjusted OR=178.02(95% CI 19.24-1647.39) and for 3 months to 6 months of age (adjusted OR= 126.39, 95% CI 17.42-917.02). In the bivariate analysis it was also found that higher proportions of infants who had fresh intestinal bleeding (60%) compared to those who did not have fresh intestinal bleeding (1.6%) suffered from dysentery within 7 days prior to death and the difference was statistically significant (p=<0.001). This finding also could be explained by the reported association of risk of dysentery with early introduction of complementary feeding among infants[67].

In chapter 10 the associations between any bleeding status of infants and maternal PIVKA-II levels for 3rd trimester of pregnancy and 3-month post partum period have been analyzed. Maternal PIVKA-II level cut off was set at 2ng/ml for the analyses. Maternal PIVKA-II level during pregnancy varies based on certain conditions during pregnancy, particularly toxemia of pregnancies, with gradual elevation of PIVKA-II related to gestational weeks being observed in healthy pregnant women[34].

In this analysis it was assumed that maternal 3rd trimester PIVKA-II levels would correspond to infants' vitamin K levels at birth and maternal 3-month post partum PIVKA-II levels would correspond to how much vitamin K infants got through lactation. It was assumed that maternal plasma PIVKA-II concentration could be a remote measure of infants' vitamin K status, and thus, could link to risk of infantile bleeding due to vitamin K deficiency.

Based on this assumption the analysis was done to evaluate the relationship in the context of the JiVitA sub-study design. Maternal 3rd trimester plasma PIVKA-II levels were measured for 293 mothers (103 mothers of infants who had bleeding and 190 mothers of infants who did not have bleeding). Similarly, maternal plasma PIVKA-II levels at 3-month post partum for 295 mothers (104 for mothers of infants who had any bleeding and 191 for mothers of infants who did not have bleeding) were measured. Laboratory analyses of 3rd trimester and 3-month postpartum PIVKA-II levels were measured for 295 mothers (1.01%), among them 272 were mothers of surviving infants (1.03%) and rest 23 were mothers of deceased infants (0.83%).

When the means of maternal 3rd trimester PIVKA-II levels among the infants who had bleeding and who did not have bleeding were compared, it appeared that the mean maternal PIVKA-II levels for infants who had bleeding were similar (ranges 1.87-2.12ng/ml) to the corresponding means of maternal PIVKA-II levels for infants who did not have bleeding in the 3rd trimester of pregnancy (2.05 ng/ml, SD±0.79). Similarly, maternal 3-month post partum plasma PIVKA-II levels did not differ statistically between groups of infants who had bleeding and who did not have for any category of time of bleeding onset. When the distribution of bleeding status of infants were examined with maternal 3rd trimester PIVKA-II level, for about 26% infants who had bleeding had maternal PIVKA-II level above 2ng/ml compared to 44.2% of infants who did no have bleeding for 2-7 days age of onset, the difference being statistically significant. For rest of the distribution of maternal PIVKA-II levels, bleeding status of infants did not differ statistically.

According to available literature, dark green leafy vegetables (DGLV) are a good source of vitamin K[14,15] and levels of vitamin K in breastmilk can be improved if mothers eat DGLV during lactation[23]. In chapter 10, the association between bleeding status of infants and maternal DGLV consumption during 3rd trimester of pregnancy and 3-month post partum period were explored. Over one third of the mothers of both types of infants did not eat any dark green leafy vegetables (DGLV) during the last seven days of both periods.

When analysis was conducted to see the association between maternal PIVKA-II levels and DGLV consumption during 3rd trimester of pregnancy and 3 month post partum, no association was found between maternal PIVKA-II levels and DGLV consumption for both time periods.

11.2 Limitations of the Study

11.2.1 Bleeding Symptoms

For the cohort of surviving infants questions on nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding (red blood in stool), dark stools, excessive bleeding during circumcision and bulging fontanel were asked during the 6 months follow up visits. Parents were asked to report the listed bleeding symptoms with the time of onset of first episodes.

For the cohort of deceased infants, during the deceased infants' verbal autopsies, parents were asked for the same set of questions on bleeding symptoms along with the time of onset of first episode.

The differences in parental reporting of bleeding symptoms between the cohort of surviving and deceased infants probably introduced bias in this study data.

The potential for bias could emerge especially from the possibility that a parent being interviewed about symptoms of the infant prior to its death could be crisply remembered, whereas questions about bleeding to a parent after a surviving child's first six months of life could be less well remembered. It was assumed that these bleeding symptoms were major events for the parents while rearing their children and that the recall accuracy would be the same for the parents of both cohorts.

But the reality was that one set of questions was asked within one month of death for deceased infants and the other set within six months of birth in the surviving infants. In rural areas, after births newborns are looked after by the grandmothers or other caregivers as the mothers remain exhausted after delivery. In that context, bleeding symptoms occurring within the first few days of birth could remain unnoticed by the mothers thus remaining underreported in this study.

As the bleeding data collection were nested in the existing data collection of an ongoing trial, it was not possible to add more variables on infantile bleeding. Data were collected only on the first episodes of bleeding with time of onset. Data on total number of episodes and duration or intensity of bleeding were not collected in this study.

Data on bulging fontanel were collected as a proxy for intracranial bleeding but as there are other reasons for this particular type of bulging, the reporting of bulging fontanel as a bleeding symptom could be an over estimate of the bleeding symptoms in this study. Data were not collected on hereditary bleeding disorders of mothers or infants in this study. This study also did not have any data on congenital anomalies of hepatobiliary system or diseases or mal-absorption syndromes.

Bleeding which could potentially occur from other routes in infancy e.g. vaginal bleeding, oral bleeding, ear bleeding etc. was also not collected in this study. Maternal drug intake during pregnancy e.g. anticonvulsants, anti-tubercular etc. are reported to be associated with early onset of infantile bleeding[10,21,23]. Data on these variables were also not collected in this study. Recommendations need to be there to consider all these data to be collected in future studies on infantile bleeding disorders.

For the deceased infants in this study mothers were asked whether the infants had any types of injury before death. But mothers were not asked whether the reported bleeding followed any injury or not. Reported bleeding symptoms were checked with the injuries suffered by the infants and found to be very low in numbers, and were not excluded, as in vitamin K deficient conditions a trivial injury could cause more bleeding[15]. For the cohort of infants who survived, mothers were not asked whether their babies suffered any injury or whether the bleeding was due to any injury.

11.2.2 Case Fatality Rates

Case fatality rates were calculated as a measure of severity of bleeding symptoms among the infants born in rural Bangladesh in this study. By text book definition, the numerator of a case-fatality rate should be restricted to the deaths among individuals who are defined as cases of a disease[69]. Although in this study it was not possible to distinguish between the deaths due to bleeding and deaths from other causes in the analysis, but based on time-to-death data presented in Chapter 7, it was assumed that bleeding when presented may have contributed to deaths in many instances. This provided basis for estimating case fatality rates associated with bleeding symptoms in the analyses.

For calculating any specific case fatality rate, the numerator was deceased infants with that specific bleeding symptom and the denominator was the sum of the numbers of infants in both the deceased and surviving cohorts reported to have had that specific bleeding symptom.

11.2.3 Exclusive Breastfeeding

Exclusive breastfeeding estimations were also based on maternal recall in this study. Exclusive breastfeeding (EBF) among the cohort of surviving infants was ascertained by combining data from historic questions posed to mothers at six months follow up visits about whether the infant was breast-fed and the timing of introducing a list of common complementary foods. Infants reported to have been breastfed at a specific age and who also had no history of receiving other foods before or at any time during the specific age interval were classified as being exclusively breastfed at that age interval. That is, classification of infants as EBF in this study was conditional on being breast fed exclusively at the age being considered and all prior age intervals.

Exclusive breastfeeding (EBF) for the cohort of deceased infants was defined in a similar way as to those who survived by combining data from historic questions posed to mothers during verbal autopsy interviews about whether the infant had been breastfed and the timing of introducing a list of common complementary foods. Infants reported to have been breastfed at a specific age and who also had no history of receiving other foods before or at any time during the specific age interval were classified as having been exclusively breastfed in that age interval. That is, classification of infants as EBF in this study was conditional on being breast fed exclusively at the age being considered and all prior age intervals.

It would have been better if the study could use identical methods of exclusive breastfeeding data collection for both the cohorts of surviving and deceased infants. The best exclusive breastfeeding data to estimate the association between bleeding and exclusive breastfeeding could be the exclusive breastfeeding data collected in reference to the time of onset of bleeding directly. This could be an option for future studies on bleeding disorders.

11.2.4 Morbidities

Morbidity data collected in this study also had different time of recall period for surviving and deceased infants. During data collection mothers were asked whether their surviving infants suffered from cough/cold, high fever, diarrhoea and dysentery in last 3 months during the 6 months follow up visits. On the other hand, mothers were asked during the verbal autopsies; whether their deceased infants suffered from cough/cold, cough with high fever, breathing difficulties, diarrhea and dysentery in the 7 days prior to death. In the data, reference time periods of morbidities were different for surviving and deceased infants. It would be better if same morbidity questions were used in relation to the time of onset of bleeding for both types of infants.

As the morbidity data were not collected in relation to the bleeding episodes, these bleeding symptoms could not be explained by temporal relationship with morbidities for both surviving and deceased infants. But, if it was assumed that the pattern of morbidities suffered by these infants were the same over different time periods, then the collected information on morbidities could be considered as a proxy of the morbidities suffered by the infants during the bleeding episodes.

11.2.5 Maternal PIVKA-II levels

In this study vitamin K levels were not directly measured either for mothers or their infants. Maternal PIVKA-II level for the 3rd trimester of pregnancy was considered as a proxy for maternal vitamin K levels (level of vitamin K transferred through placenta), thus level of vitamin K for neonates. It would have been better if vitamin K levels of cord blood samples were measured as this procedure is reported in relevant studies[65,70]. Maternal blood samples at 3-month post partum were analyzed to estimate the PIVKA-II levels. Maternal 3-month post partum PIVKA-II levels were considered as a proxy for the amount of vitamin K babies were getting through lactation. Breastmilk was not used to measure the phylloquinone levels in this study, which could be an option for future studies on this topic.

Breastmilk samples or maternal blood samples during bleeding episodes of infants could provide a better and more accurate estimation to measure association between maternal Vitamin K levels and infantile bleeding. Small sample size for maternal PIVKA-II levels did not allow the study to measure the association for individual bleeding symptoms, alternate to that of any bleeding symptom that was analyzed.

In Bangladesh dark green leafy vegetables (DGLV) availability and consumption are affected by seasonal variations. Relatively small sample size for maternal PIVKA-II levels did not allow this study to further analysis for maternal PIVKA-II levels and DGLV consumptions. In absence of any direct estimates of vitamin K levels of infants, indirect estimates through maternal DGLV consumption and PIVKA-II levels were used in this study.

11.3 Control of Biases

To minimize recall biases female interviewers were adequately trained on standardized interview techniques. The interviewers were trained on each of the questions on bleeding separately. They were trained on the operational definitions (Annexure-IV), extent of probing, coding and cross checking of the reported data. Field testing of the questions on bleeding was done to make sure the rural mothers understood the questions fully. For this purpose local dialects were incorporated in the questionnaires. Also to minimize recall biases, 6 months follow ups were completed within 28 weeks of age for the surviving infants. Similarly, most of the verbal autopsies were completed within one month of deaths of deceased infants. Stratified analyses were conducted based on the time of onset of bleeding for individual bleeding e.g. nasal bleeding, bruising, umbilical bleeding, fresh intestinal bleeding and for any combination of bleeding with other explanatory variables e.g. breastfeeding, infantile characteristics, morbidities etc. separately for surviving and deceased infants as a means to assess the consistency in association and controlling for potential biases and confounders.

11.4 Representativesness

Probably this study analyzed one of the largest samples (N=29844) to explore infantile bleeding in a community setting. The adjacent areas of river (char area) and urban pockets of Gaibandha were excluded for better representation. The trial set up enabled to track infants to minimize the loss to follow ups in this study. Only those babies whose families migrated permanently outside of the study area were lost to follow-up.

Considering the above factors the result of this study can be generalized for other rural areas of Bangladesh.

11.5 Recommendations and Conclusion

Reported infantile bleeding, consistent with clinical VKDB, is not uncommon in rural Bangladesh and is found to be associated with extremely high mortality, especially in neonatal life. Findings of this study revealed that all the factors that are known to be the risk factors of vitamin K deficiency bleeding e.g. exclusive breastfeeding, male gender, prematurity, diarrhoea etc. were also found to be associated with increased risks of bleeding in this rural Bangladeshi population. Maternal vitamin K deficiency, measured by plasma PIVKA-II concentration in this study, was not found to be associated with infant bleeding. Still, because maternal status may not adequately reflect vitamin K status of infants, vitamin K deficiency remains a most likely explanation for bleeding risk in this and other rural populations.

Bleeding during infancy could occur for many different reasons e.g. hemophilia, thrombocytopenia, disseminated intravascular coagulation, necrotizing enterocolities, coagulopathy etc. To sort out the vitamin K deficiency bleeding among the infants in this population, it is needed to address all other conditions responsible for infantile bleeding in subsequent studies. Knowing the accurate reasons of these infantile bleeding problems, awareness programs can be formulated to train the community health workers especially traditional birth attendants on infantile bleeding. This will enable them to create awareness in parents so that they can seek immediate care to avoid morbidity and mortality related to bleeding disorders of their infants.

According to the literature, the condition manifested by bleeding from one or more body sites in infants can be effectively prevented by administration of vitamin K: 0.5-1 mg phylloquinone intramuscularly or 2.0 mg orally, within 6 hours of birth.

Based on this study findings, a randomized controlled trial may well be justified to test the efficacy of vitamin K supplementation at birth in preventing vitamin K deficiency bleeding among infants born in rural Bangladesh.

References

1.	Sutor AH. New aspects of Vitamin K prophylaxis. Section of Pediatric Hematology, Universitats-Kinderklinnik Freiburg, Freiburg, Germany. Sutor@kikli-uni-freiburg.dc. PMID:14703597 [PubMed-indexed for MEDLINE]
2.	Barbara A. Bowman and Robert M. Russell. Present Knowledge in Nutrition. Eighth Edition. ILSI, International Life Science Institute, ILSI press, Washington DC, USA.
3.	Sutor AH, von Kries R, Cornelissen EAM, McNinich AW, Andrew M, on behalf of the ISTH Pediatric/Perinatal Subcommittee: Vitamin K deficiency bleeding (VKDB) in infancy. Thromb Haemost 1999;81:456-461.
4.	http://www.medsafe.govt.nz/Profs/PUarticles/vitk.htm . Vitamin K Prophylaxis in the Newborn. Prescribers Update Article Prescribers Update No. 21:36-40.
5.	Martin John Shearer and Hui-Feng Zhang. Early infant vitamin K deficiency: extent, health consequences and approaches to prophylaxis. Micronutrient Deficiencies in the First Months of Life. Nestle Nutritional Workshop Series Pediatric Program. Nestle Nutrition, Vol 52. Page 192.
6.	D'Souza, Rao SD. Late hemorrhagic disease in newborn. Indian Pediatr. 2003 Aug; 40(8): 793-45
7.	Pooni PA, Singh D, Singh H, Jain BK. Intracranial hemorrhage in late hemorrhagic disease of the newborn. Department of Pediatrics, Dayanand College and Hospital, Ludhiana, Punjab, India. poonia@yahoo.com. PMID: 12657759 [PubMed-indexed for MEDLINE]
8.	Chuansumrit A, Isarangkura P, Hathirat P, and Vitamin K study group: Vitamin K deficiency bleeding in Thailand: A 32- year history. South Asian J Trop Med Public Health 1998;29: 649-654.
9.	Choo KE, Tan KK, Chuah SP, et al. Haemorrhagic disease in the newborn and older infants: a study of hospitalized children in Kelantan, Malaysia. Ann Trop Paediatr 1994;14:231-237.
10.	Zhou F, He S, Wang X. An epidemiological study on vitamin K deficiency bleeding in infants under six months. Zhonghua Yu Fang Yi Xue Zhi. 2002 Sep; 36(5): 305-7 PMID: 12411188[PubMed-indexed for MEDLINE]

11.	Cesar G. Victora MR, PhD, and Philip Van Haecke, BBL, MPA. Vitamin K Prophylaxis in Less Developed Countries: Policy Issues and Relevance to Breastfeeding Promotion. American Journal of Public Health. 1998, Vol.88: 203-209.
12.	N Danielsson, D P Hoa, N V Thang, T Vos, P M Loughnan. Intracranial Hemorrhage due to late onset vitamin K deficiency bleeding in Hanoi, Vietnam. Arch Dis Child Fetal Neonatal Ed 2004, 89:F546-F1550
13.	Behrman et al. 17th edition. Nelson text book of pediatrics. An imprint of Elsevier. The Curtis center. Independence Square West. Philadelphia, Pennsylvania 19106.
14.	http://www.healthatoz.com/healthatoz/Atoz/ency/vitamin_k_deficiency.isp. Vitamin K deficiency.
15.	Sarah L Booth, James A Sadowski and Jean A T Pennington. Phylloquinone (Vitamin K1) content of foods in the US Food and drug administration's total diet study. J. Agric. Food Chem., Vol 43. No 6, 1995.
16.	http://www.nutritionupdates.org . Nutrition Research Review. Arbor Clinical Research Update#201: Vitamin K and osteoporosis.
17.	http://www.gpnotebook.co.uk/simplepage.cfn?ID=-831848442&linkID=59864&cook=yes. Vitamin K- General Practice Notebook.
18.	Pankaj P, Mageda M. Vitamin K Deficiency http://www.emedicine.com/med/topic2385.htm.
19.	Food and Nutrition Board, Institute of Medicine. Vitamin K. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington D.C.: National Academy. Press; 2001:162-196. (National Academy Press)
20.	http://lpi.oregonstate.edu/infocenter/vitamins/vitaminK/printk.html. Micronutrient Information Center. Vitamin K. The Linus Pauling Institute.
21.	Eugenio G., Ronaldo J M S, Jorge H B F. Intracranial hemorrhage in infants due to vitamin K deficiency –report two. J Pediatr (Rio J) 2000; 76(3): 233-6.
22.	Waddell WW, Guerry D. The role of vitamin K in the etiology, prevention, and treatment of hemorrhage in the newborn infant. J Pediatr 1939;15:802-11
23.	http://www.vitaminconnection.com/NIO/ConsSupplements/VitaminKcs.html. Vitamin K.

24.	Zerrin O, Ayse S, Hakan D. Inherited Vitamin K Deficiency Report and Review of Literature. Yonsei Medical Journal. Vol.44, No. 5, pp. 923-927, 2003
25.	Vitamin K- A neglected health factor. Micronutrients and Health. Nutriview 2002/4.
26.	http://ctds.info/vitamink.html . Vitamin K
27.	Guylaine F. The Vitamin K-dependant Proteins: An update. Lead Review Article. August 1998:223-230.
28.	Lane PA, Hathaway WE: Vitamin K in infancy. J Pedatr 1985; 106:351-359.
29.	Sutherland JM, Glueck HI, Gleser G. Hemorrhagic disease of the newborn. Breastfeeding as a necessary factor in the pathogenesis. Am J Dis Child 1967; 113:524-33.
30.	Hanawa Y, Maki M, Murata B, et al: the second nation-wide survey in Japan of vitamin K deficiency in infancy. Eur J Pediatr 1988; 147:472-477.
31.	Loughnan PM, McDougall PN: Epidemiology of late onset hemorrhagic disease: A pooled data analysis. J Paediatr Child Health 1993;29:177-181.
32.	Figueiredo RC, Norton RC, Lamounier JA, Leao E. Late hemorrhagic disease of newborn: case report. Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. PMID: 14685365 [PubMed]
33.	Aydinli N, Caliskan M, Karabocuoglu M, Baysal S, Ozmen M. Vitamin K deficiency—late onset intracranial haemorrhage. Department of Pediatrics, Institute of Child Health, Istanbul University, Turkey. PMID:10726592 [PubMed-indexed for MEDLINE]
34.	Tomizo Nishiguchi, M.D., Ph.D., Kaoru Massuyama, M.D., Takao Kobayashi, M.D., Ph.D, and Naohiro Kanayama M.D., Ph.D . Des-Gamma-Carboxyprothrombin (PIVAK-II) levels in maternal serum throughout gestation. Siminars in Thrombosis and Hemostasis, Volume 31, Number 3, 2005.
35.	Dam H, Tage-Hansen E, Plum P. Vitamin-K lack in normal and sick infants. Lancet 1939;ii: 1157-61
36.	Nygaard KK. Prophylactic and curative effect of vitamin K in hemorrhagic disease of the newborn (hypothrombnemia hemorrhagica neonatorum). Acta Obstet Gynaecol Scand 1939;19:361-70.
37.	Lehmann J. Vitamin K as a prophylactic in 13,000 babies. Lancet 1944;i:493-4 (see also i:506-8 and ii:737-8).

38.	Report of a joint FAO/WHO expert Consultation. Bangkok, Thailand. FAO/WHO 2002. Human Vitamin and Mineral Requirements. Chapter 10. Vitamin K. FAO corporate document repository. http://www.fao.org.
39.	Bhanchet, P. et al. 1977. A bleeding syndrome in infants due to acquired prothrombin complex deficiency: a survey 0f 93 affected infants. Clin. Pedaitr., 16:992-8.
40	McNinch, A.W., Orme, R.L' E. & Tripp, J.H. 1983. Haemorrhagic disease of the newborn returns. *Lancet*, i: 1089-90.
41	Lulsseged S. Hemorrhagic disease of the newborn: a review of 127 cases. Ann Trop Paediatr 1993;13:331-6.
42	http://www.gpnotebook.co.uk/simplepage.cfm?ID=1463091245&linkID=17068&cook=yes. Risk factors-General Practice Notebook.
43	Golding J, Paterson M, Kinlen LJ, Factors associated with childhood cancer in a national cohort study. Br. J Cancer 1990;62:304-8.
44.	Golding J, Greenwood R, Birmingham K, Mortt M. Childhood cancer, Intramuscular vitamin K, and pethidin given during labour. BMJ 1992;305:341-6.
45	Ansell P, Bull D, Roman E. Childhood leukaemia and intramuscular vitamin K: finding from a case-control study. BMJ 1996;313:204-5.
46	Ekelund H, Finnstrom O, Gunnarskog J, Kallen B, Larsson Y. Administration of vitamin K to newborn infants and childhood cancer. BMJ 1993;307:89-91.
47	Olsen JH, Hertz H, Blinkenberg K, Verder H. Vitamin K regimens and incidence of childhood cancer in Denmark. BMJ 1994;308:895-6.
48	Von Kries R, Gobel U, Hachmeister A, Kaletsch U, Michaelis J. Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany. BMJ 1996;313:199-203.
49.	Klebanpff MA, Read JS, Mills JL, Shiono PH. The risk of childhood cancer after neonatal exposure to vitamin K. N Engl J Med 1993;329:905-8.
50.	Controversies Concerning Vitamin K and the newborn. Committee on Fetus and Newborn. Pediatrics Vol. 112 No. 1 July 2003, pp.191-192.
51.	Jane S P, Gerald D, Pat B, Marry Kroll. Case-control studies of relation between childhood cancer and neonatal vitamin K administration. BMJ 1998;316:178-184.

52.	Judith Podja and Laura Kelly, Low Birth Weight, ACC/SCN Nutritional policy paper #18. Sept 2000. A report based on the International Low Birth Weight Symposium and Workshop held on 14-17 June at the ICDDRB.
53.	Unicef-Bangladesh-Statistics. http://www.unicef.org/infobycountry/bangladesh_bangladesh_statistics.html
54.	M de Onis, M Blossner and J Villar. Worldwide distribution IUGR-LBW. Levels and Patterns of Intrauterine Growth Retardation in Developing Countries. WHO Collaborative Study on Maternal Anthropometry and Pregnancy Outcomes, 1995 (WHO, 1995b). http://www.unu.edu/unpress/food2/unido3e
55	Helen Keller International and Institute of Public Health Nutrition (2006). Bangladesh in Facts and Figures: 2005 Annul Report of the Nutritional Surveillance Project. Dhaka, Bangladesh, Helen Keller International/
56.	M. Rashid, A.B. Labrique, A.A.Shamim, R.W. Klemm, P. Christian , K.P. West, Jr. Early Complementary Feeding is Associated with Increased Risk of Morbidity. Presented at the 2nd National Breastfeeding Conference, August 2006. Dhaka, Bangladesh
57.	Halida H. Akhter, Mohsena Akthter and Kazi Mahbubur Rashid Azad. A National Baseline Survey to Assess the Breastfeeding Practices in Bangladesh. BIRPERHT Publication No. 116, ISBN: 984-8227-01-6, 1998.
58.	Keith P West Jr, Parul Christian, Rolf Klemm, Alain Labrique, Mahbubur Rashid , Abu Ahmed Shamim, Joanne Katz and Alfred Sommer. The JiVitA Bangladesh Project: Research to improve nutrition and health among mothers and infants in rural South Asia. Sight and Life, Newsletter 1/2006. PO box 2116, 4002 Basel, Switzerland. http://sightandlife.org
59.	Kojima T et al, Acta Paediatr. Vitamin K concentrations in the maternal milk of Japanese women. 2004; 457-63.
60.	Keith P West Jr., Joanne Katz, Subarna K Khatry, Steven C LeClerq, Elizabeth K Pradhan, Sherada R Shrestha et al. Double blind, cluster randomized trial of low dose supplementation with vitamin A or β carotene on mortality related to pregnancy in Nepal. BMJ 1999; 318:570-575. www.bmj.com

61.	Lakshmi Rahmathullah, James M Tielch, R D Thulasiraj, Joanne Katz, Christian Coles, Sheela Devei, Rajesh John et al., Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomized trial in Southern India BMJ 2003: 327:1-6. www.bmj.com
62.	Selvin S. Statistical analysis of epidemiological data, Third edition, Oxford University Press 2004, page 84-88.
63.	StataCorp.2005. Stata Statistical Software: Release 9.0. College Station, TX: Stata Corporaton.
64.	Asserachrom PIVKA II. Enzyme Immunoassay of PIVKA-II. Diagnostica Stago, 9, rue des Freres Chausson, 92600 ASNIERES-SUR-SEINE (FRANCE)
65.	Frank R. Greer, MD, Sharon Marshall, RN, Jennifer Cherry, BS, and John W. Suttie PhD. Vitamin K status of lactating mothers, human milk, and breastfeeding infants, Pediatrics Vol. 88 No. 4 October 1991
66.	National Research Council, 1989. Recommended Dietary Allowances, 10th edition. Washington DC: National Academy Press.
67.	M. Rashid, A.B. Labrique,A.A. Shamim, R. Klemm, P. Christian, K.P. West, Jr. Early Complementary Feeding is Associated with Increased Risk of Morbidity. National Breastfeeding conference. 19-20 Aug 2006
68.	http://www.racp.edu.au/hpu/paed/vitk/bg.htm. Joint Statement and Recommendations on Vitamin K Administration to newborn infants to prevent Vitamin K deficiency bleeding in infancy. Health and Social Policy.
69.	Leon Gordis. Prof. Epidemiology, Johns Hopkins University, USA. Epidemiology. ISBN 0-7216-5137-2. W.B. Saunders Company.
70.	Edmund Hey. Effect of maternal anticonvulsant treatment on neonatal blood coagulation. Arch Dis Child Fetal Neonatal Ed. 1999; 81: F208-F210 (Nov).
71.	http://www.icddrb.org/pub/publication.jsp?classificationID=46&pubID=5269. Findings of PROJAHNMO-1 and PROJAHNMO-2 Projects. 2003. ICDDR, B Publications.
72.	Humphrey JH, Ichord RN. Safety of vitamin A supplementation of postpartum women and young children. *Food Nutr Bull* 2001;22:311-9.

The JiVitA Bangladesh Project: Research to improve nutrition and health among mothers and infants in rural South Asia

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More than half of pregnant women in rural South Asia are likely to be affected by multiple micronutrient deficiencies (1) presumably arising from demands of pregnancy and lactation superimposed on diets chronically lacking in vegetables, fruit, and animal products (2, 3). This same region also harbors risks of mortality that claim over 40% of all maternal and infant deaths in the world each year. Deficiencies in vitamin A, iron, folate and other nutrients can have deleterious effects on the health of mothers and their offspring and may account for substantial maternal morbidity and mortality in undernourished and underserved settings (4–6), yet much remains to be known about the efficacy of micronutrient supplementation in improving health and the public health approaches that optimize benefit, minimize risk and remain feasible and low cost.

The JiVitA Bangladesh Project (the term "JiVitA", pronounced jiveeta, is based on the Bangla word jibheetoh, which means "alive") was established in 1998 to improve the health and survival of women of reproductive age, infants, and young children in South Asia through community-based micronutrient trials and supportive epidemiologic research. The Project is a research component of the Government of Bangladesh's Ministry of Health and Family Welfare under its National Integrated Population and Health Program (NIPHP) which is jointly administered with the United States Agency for International Development (USAID). The Project seeks to evaluate the efficacy and safety of micronutrient interventions for reducing maternal morbidity and mortality, fetal malnutrition and loss, and infant morbidity and mortality. It is motivated by a need to inform and guide policies and programs in this area of public health. The first major trial, called JiVitA-1, began in August 2001 and is ongoing. This 67,000-pregnancy, placebo-

Figure 2. Mother participating in JiVitA-1 receiving a weekly capsule from a field worker.

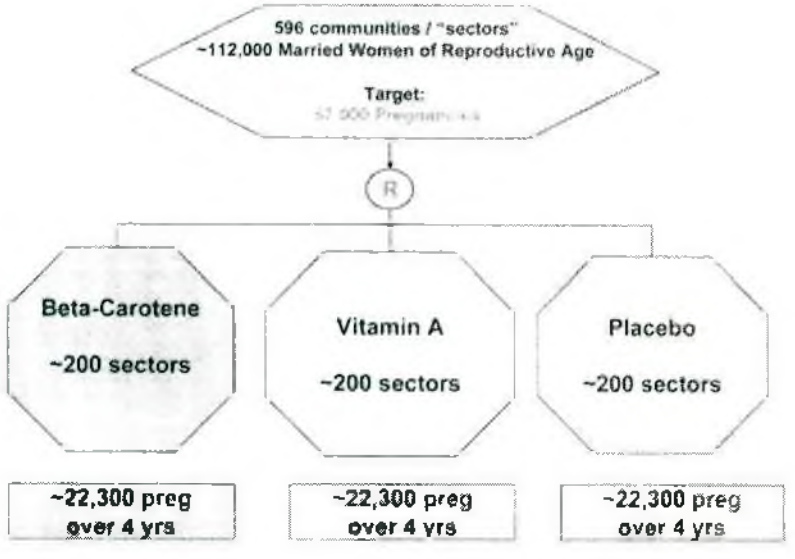

Figure 1. JiVitA-1 is a cluster-randomized, double-masked, placebo controlled community trial

controlled trial is testing the effects of maternal supplementation with the weekly equivalent of a recommended dietary allowance (RDA, estimated for pregnant or lactating women to be ~23,300 IU (7000 µg retinol equivalents)) of vitamin A, either preformed or as provitamin "-carotene, on mortality of women related to pregnancy, and on fetal loss and infant mortality (Figure 1). In doing so, JiVitA-1 is seeking to extend previous findings from a similar trial in Nepal to a broader South Asian context (Figure 2). This earlier trial observed a ~40% reduction in mortality of women related to pregnancy (7–8) (Figure 3). Although there was no overall effect on infant mortality (9), there appeared to be a survival advantage to babies born to women at risk of night blindness (10). A second ongoing placebo-controlled trial, called JiVitA-2, is nested into the first (Figure 4). This study seeks to confirm previous work in Indonesia (11) and India (12) that newborn receipt of ~50,000 IU of vitamin A can reduce mortality in South Asian infants. The trial is designed to enroll ~23,100 infants born to JiVitA-1 mothers, supplement them within the 1st two days of life and follow their health and survival through six months of age (Figure 5). Evaluating effects of interventions on mortality typically require enrolling, supplementing, and following large numbers of subjects, as in these two trials.

Located in the rural, rice-growing, population-dense northern districts of Gaibandha and Rangpur, the JiVitA Project covers 19 unions with an area of ~650 km² and population of nearly 650,000 people (Figure 6). The area in which JiVitA operates lies at roughly the 25th percentile of the country with regard to many of its health, nutrition, vital, socioeconomic and development statistics (13). Since 1998, a joint team of researchers from Johns Hopkins University (USA) and Bangladesh has developed this research site. This process has included (a) establishing a network of national and local institutional linkages; (b) recruiting and training over 850 staff, ~90% of whom are local women, to fill technical, administrative and logistical needs; (c) mapping and addressing over 130,000 households, adapting maps drawn from aerial photography in the 1930s that are now supported by a global positioning system (GPS)-based geographic information system (GIS) to enhance field efficiency and epidemiologic studies; and (d) establishing a network of 70 field offices, a central field management station, biospecimen processing laboratory, and a project headquarters housing administrative, data management and GIS facilities. The JiVitA data management center has 24 staff and is capable of processing up to 20,000 records each week (Figure 7).

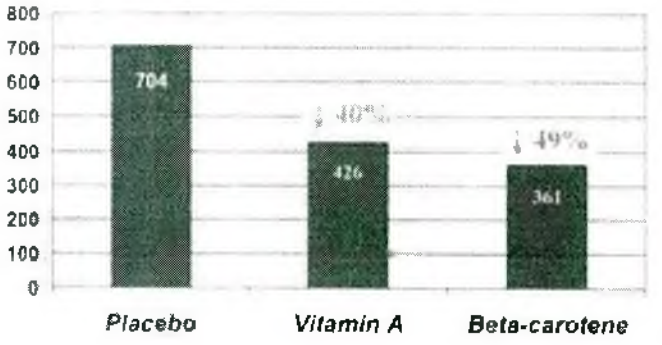

Figure 3. Maternal mortality rate (per 100,000) in response to vitamin A (7000 µg RE/wk) and "-carotene (42 mg/wk) in Nepal.

The need for units of randomization smaller than a union led us to create 596 "sectors" of similar size (each with ~250 households) that also serve as individual 'work units" for each of our sector-based local staff (Figure 2). In order to launch JiVitA-1 in August 2001, over 120,000 women of reproduc-

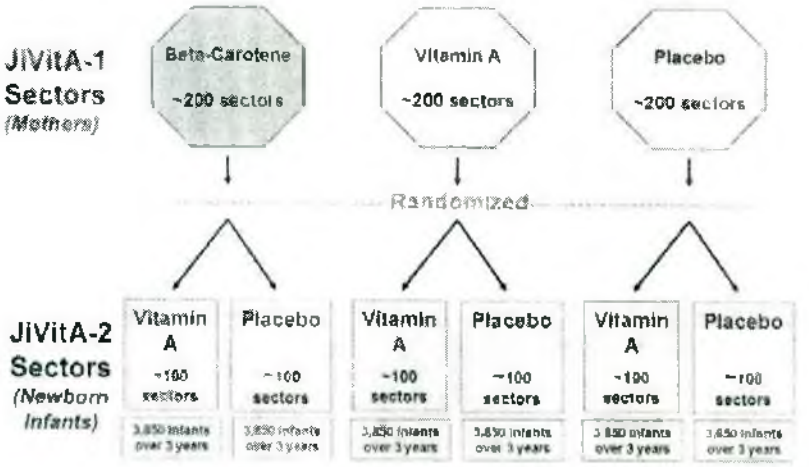

Figure 4. The JiVitA-2 trial is designed to enroll about 23,100 infants born to JiVitA-1 mothers.

Figure 5. A newborn receiving a JiVitA-2 study capsule.

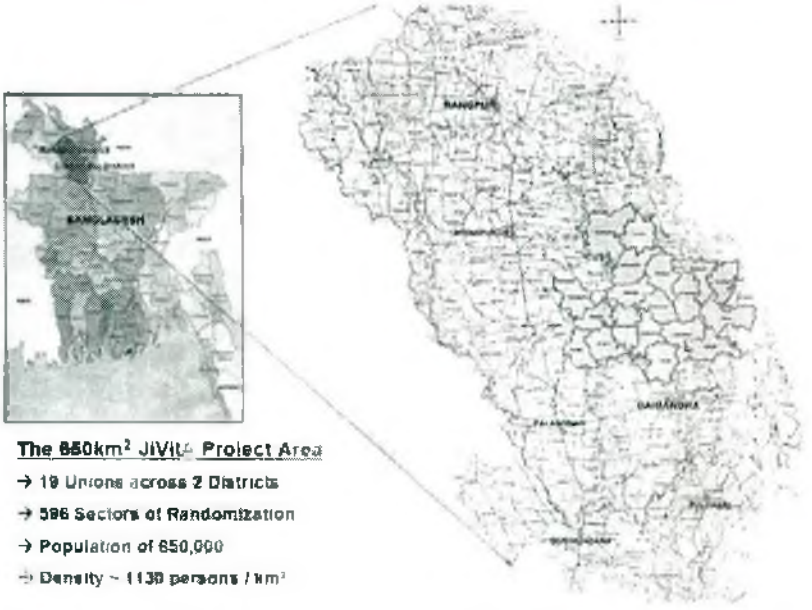

Figure 6. The JiVitA study area is located in 19 unions (highlighted to the right), mostly in the District of Gaibandha. The area is further divided into nearly 600 "sectors" (not shown) that serve as units of randomization and staff assignment.

Figure 7. The JiVitA data management center in Rangpur enters up to 20,000 records each week at an error rate of <4 per 10,000 keystrokes, interacts weekly with the field to solve queries and maintains a GIS mapping unit.

tive age were initially registered and a five-weekly, home-based surveillance system was implemented that annually detects ~5000 newly married women and recruits into the trial up to 18,000 1st trimester pregnancies that are confirmed by urine testing. The system is complemented by a weekly home-visiting program during which consenting pregnant women are given study supplements under supervision, and pregnancy outcomes and births are recorded. Within two days of birth, infants are given a JiVitA-2 supplement, consisting of either 50,000 IU of vitamin A or a placebo, and assessed for size by anthropometry in the home. Vital events of enrolled mothers and infants continue to be monitored during weekly home visits for the 1st three months after childbirth, and periodically thereafter.

Large trials offer opportunities to conduct enhanced substudies to assess changes in more involved indicators of nutritional status, morbidity and function that can be evaluated in relation to an intervention. These intensive protocols aim to complement periodic interview-based assessments of morbidity and diet carried out in the general trial population. For example, in a designated substudy area in JiVitA, involving ~3% of all pregnant women, we conduct an array of maternal assessments during the 1st and 3rd trimester visits and at three months postpartum. These include anthropometry, phlebotomy for later vitamin A, carotenoid, and other micronutrient, antioxidant and immune assays, urine collection for iodine and other analytic studies, vaginal smears for assessments of bacterial vaginosis risk and response, and maternal body composition analysis by bioelectrical impedance. Substudies in infants obtain detailed anthropometry at birth, 3 and 6 months of age (Figure 8) and seek to reveal potential disease

mechanisms that may be responsive to supplementation of either the mother or infant. For example, one JiVitA-2 substudy is assessing rates of nasopharyngeal colonization with *Haemophilus influenza B* and *Streptococcus pneumoniae* at three months of age, both being causes of acute respiratory infections in early infancy against which vitamin A may offer some protection (14). Another study is being planned to examine effects of vitamin A on neonatal sepsis and related complications. Across the larger trial population, a field worker-based birth defect surveillance system, backed by physician exam and digital-photography, is being tested and evaluated for its ability to generate reliable estimates of anatomical defects, for rate estimation and responses to this or subsequent interventions.

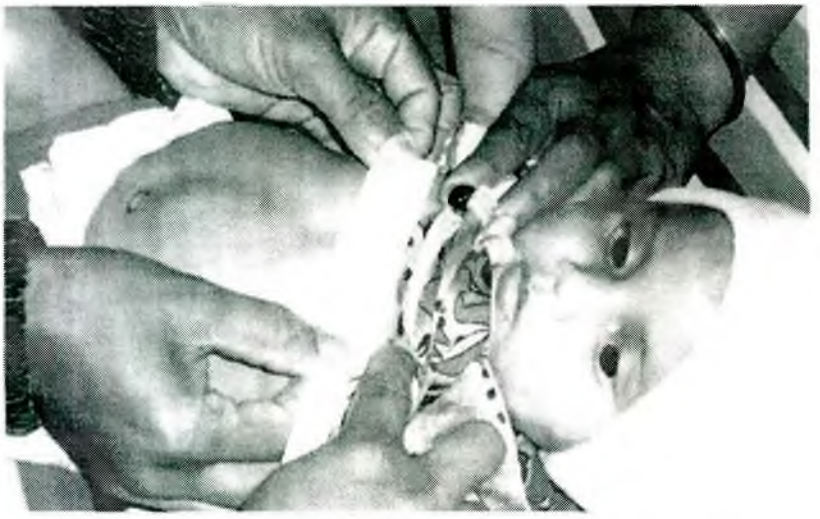

Figure 8. A JiVitA-2 infant in the substudy area being measured for chest circumference using an adapted "Zerfas" insertion tape.

The JiVitA Project continues to learn a great deal from meeting the challenges of setting up a modern, collaborative research program in a rural South Asian setting – one that is capable of conducting large nutrition and health care intervention trials that can inform policy. The current trials are due to be completed during 2007. Additional research is being planned, guided by emerging findings elsewhere in the region (15–17), that may help to advance maternal and infant micronutrient deficiency prevention in South Asia in the future.

The JiVitA Project is implemented by the Center for Human Nutrition in the Department of International Health of the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland (USA) in collaboration with several expert partners, including the Institute of Nutrition at Mahidol University in Thailand, the Institute of Nutrition and Food Sciences, Dhaka University, the Shishu (Children's) Hospital in Dhaka, the Institute for Child and Maternal Health in Dhaka and the Bangladesh Atomic Energy Commission in Dhaka. Protocols

for all JiVitA trials and substudies are reviewed and approved by the Johns Hopkins Committee on Human Research and the Bangladesh Medical Research Committee. The JiVitA Project is made possible through the generous support of the Office of Health, Infectious Diseases and Nutrition, USAID (Washington DC, USA), the USAID Mission in Dhaka, The Bill & Melinda Gates Foundation (Seattle, WA, USA) and the Government of Bangladesh, with additional financial and technical assistance from SIGHT AND LIFE and the SIGHT AND LIFE Research Institute (Baltimore, MD, USA), the Canadian International Development Agency and Micronutrient Initiative (CIDA, Ottawa, Canada), the Nutrilite Health Institute of Amway Corporation and the Access Business Group (Buena Park, CA, USA).

References

1. Jiang T et al. (2005). Micronutrient deficiencies in early pregnancy are common, concurrent, and vary by season among rural Nepali pregnant women. J Nutr 135:1106–1112.
2. Ahmed F et al. (2003). Anaemia and vitamin A deficiency in poor urban pregnant women of Bangladesh. Asia Pac J Clin Nutr 2:460–466.
3. Khan MR and Ahmed F. (2005). Physical status, nutrient intake and dietary pattern of adolescent female factory workers in urban Bangladesh. Asia Pac J Clin Nutr 14:19–26.
4. Bhaskaram P. (2002). Micronutrient malnutrition, infection, and immunity: an overview. Nutr Rev 60:S40–S45.
5. Christian P. (2002). Maternal nutrition, health, and survival. Nutr Rev 60:S59–S63.
6. West KP Jr. (2004). Vitamin A deficiency as a preventable cause of maternal mortality in undernourished societies: plausibility and next steps. Intl J Gynecol Obstet 85:S24–S27.
7. West KP Jr. et al. and the NNIPS-2 Study Group (1999). Double blind, cluster randomised trial of low dose supplementation with vitamin A or β-carotene on mortality related to pregnancy in Nepal. BMJ 318:570–575.
8. Christian P et al. (2000). Vitamin A or β-carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. J Nutr 130:2675–2682.
9. Katz J et al. (2000). Maternal low-dose vitamin A or β-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. Am J Clin Nutr 71:1570–1576.
10. Christian P et al. (2001). Maternal night blindness increases risk of infant mortality in the first 6 months of life in Nepal. J Nutr 131:1510–1512.
11. Humphrey JH et al. (1996). Impact of neonatal vitamin A supplementation on infant morbidity and mortality. J Ped 128:489–496.
12. Rahmathullah L et al. (2003). Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. BMJ 327:254–259.
13. UNICEF. Progotir Pathey 2003. On the road to progress. Dhaka: Bangladesh Bureau of Statistics 2004.
14. Coles CL et al. (2001). Vitamin A supplementation at birth delays pneumococcal colonization in South Indian infants. J Nutr 131:255–261.
15. Christian P et al. (2003). Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal. A double-masked randomized community trial. BMJ 326:571–576.
16. Christian P et al. (2003). Effects of maternal micronutrient supplementation on fetal loss and infant mortality: a cluster-randomized trial in Nepal. Am J Clin Nutr 78:1194–1202.
17. Christian P et al. (2005). Antenatal micronutrient supplements in Nepal. Lancet 366:711–712.

Infant 6-Month Postpartum Form (I6MOP)

Week of Interview: ☐☐☐ Date: ☐☐ - ☐☐ - ☐☐
dd *mm* *yy*

Worker ID: ☐☐☐☐ Initials _____ ☐☐☐

SECTION A: IDENTIFIERS/ADDRESSES

(Note to FI: Confirm name and identifiers of the respondent.)

TL Complete:

A

Union : ☐☐☐ Mauza : _____ TL PIN: ☐☐

Sector: ☐☐☐ HH: ☐☐☐☐ Woman's ID: ☐

Name: _____ Husband's Name: _____

CID: ☐ Child Name: _____ Sex: ☐

1=Male
2=Female

Relation of respondent to child: ☐

1=Mother
2=Father
3=Grandmother
4=Grandfather
5=Other (Specify:_____)
9=Don't know

Form Status: ☐

1= Form completed
2= Not met by 28 wk of age
5= Child adopted
6= Refused interview
7= Permanently moved → **STOP**

8= Child died → **STOP: Complete IVBA**

==========

(Note to FI: If this child's name is known, replace "this child" with the actual name in the questions below.)

SECTION B: MORBIDITY

B

1. In the past 3 months has this child had a cough, cold, or had difficulty breathing?

☐ 0=No (Go to 2)
1=Yes (Go to 1a)
9=Don't know (Go to 2)

1a. In the past 3 months, how many times has this child had a cough, cold or had difficulty breathing?

☐ 1-7=No. times
8=8 or more times
9=Don't know

1b. Of these ____ times, I will now ask you about the worst time. During the worst time of cough, cold or difficulty breathing...

i. ...did this child have cough ?

☐ 0=No
1=Yes
9=Don't know

ii. ... was this child breathing faster than usual?

☐ 0=No
1=Yes
9=Don't know

iii. ...did this child have chest indrawing?

☐ 0=No
1=Yes
9=Don't know

iv. ...did this child make wheezing sounds when breathing?

☐ 0=No
1=Yes
9=Don't know

v. ...did this child make grunting sounds when breathing ?

☐ 0=No
1=Yes
9=Don't know

vi. ...did this child have high fever (hot to touch) ?

☐ 0=No
1=Yes
9=Don't know

vii. ...did this child have 4 or more loose, watery stools per day ?

☐ 0=No
1=Yes
9=Don't know

viii. ...did this child have bloody stools ?

☐

0=No
1=Yes
9=Don't know

ix. ....how many days did this worst time of cough, cold or difficulty breathing last ?

☐☐

01-97=No. of days
98=98 or more days
99=Don't know

x. ...how old was this child (in completed months)?

☐

3-6=Number of months
9=Don't know

xii....where or by whom was this child treated ?

☐

0=Not treated
1=Home remedy
2=Shaman (Religious Healer)
3=Homeopath/Ayurveda/Kabiraj
4=Medicine shop
5=Village doctor
6=Paramedic (FWV,MA,HA, SACMO, Pharmacist ,SC,FWC,CC, etc.)
7=Doctor(MBBS)/Clinic
8=Hospital(THC)
9=Don't know

1c. How many days in the past 7 days has this child had a cough, cold or difficulty breathing?

☐

0=None
1-7=No. of days
9=Don't know

2. In the past 3 months has this child had any day with 4 or more loose watery stools or diarrhea?

☐

0=No (Go to 3)
1=Yes (Go to 2a)
9=Don't know (Go to 3)

2a. In the past 3 months, how many times did this child have 4 or more loose watery stools or diarrhea per day ?

☐

1-7=No. times
8=8 or more times
9=Don't know

2b. Of these ____ times, I will now ask you about the worst time.
During the worst time of loose watery stools or diarrhea...

i. ...how many days did the loose watery stools or diarrhea last ?

☐☐

01-97= No. of days
98=98 or more
99=Don't know

B

ii. ...what was the maximum number of stools per day ?

☐

1-7=No. of stools
8=8 or more
9=Don't know

iii. ...where or by whom was this child treated?

☐

0=Not treated
1=Home remedy
2=Shaman (Religious Healer)
3=Homeopath/Ayurveda/Kabiraj
4=Medicine shop
5=Village doctor
6=Paramedic (FWV,MA,HA, SACMO, Pharmacist ,SC,FWC,CC, etc.)
7=Doctor(MBBS)/Clinic
8=Hospital(THC)
9=Don't know

iv....how old was this child (in completed months)?

☐

3-6=Number of months
9=Don't know

2c. How many days in the past 7 days has this child had 4 or more loose watery stools ?

☐

0=None
1-7=No. of days
9=Don't know

3. In the past 3 months has this child had any bloody stools?

☐

0=No (go to 4)
1=Yes (go to 3a)
9=Don't know (go to 4)

3a. In the past 3 months, how many times did this child have bloody stools?

☐

1-7=No. times
8=8 or more times
9=Don't know

3b. Of these ____ times, I will now ask you about the worst time.
During the worst time of bloody stools_____

I. ...how many days did the bloody stools last ?

☐☐

01-97= No. of days
98=98 or more days
99=Don't know

ii. ...what was the maximum number of bloody stools per day ?

☐

1-7= Number of stools
8=8 or more
9=Don't know

B

iii....did this child have a high fever (hot to touch) ?

☐

0=No
1=Yes
9=Don't know

iv. ...where or by whom was this child treated ?

☐

0=Not treated
1=Home remedy
2=Shaman (Religious Healer)
3=Homeopath/Ayurveda/Kabiraj
4=Medicine shop
5=Village doctor
6=Paramedic (FWV,MA,HA, SACMO, Pharmacist ,SC,FWC,CC, etc.)
7=Doctor(MBBS)/Clinic
8=Hospital(THC)
9=Don't know

v....how old was this child (in completed months)?

☐

3-6=Number of months
9=Don't know

3c. How many days in the past 7 days did this child have bloody stools?

☐

0=None
1-7=Number of days
9=Don't know

4. In the past 3 months has this child had a high fever, that is, this child was hot to the touch?

☐

0=No (go to Section C)
1=Yes (go to 4a)
9=Don't know (go to Section C)

4a. In the past 3 months, how many times did this child have high fever (hot to touch)?

☐

1-7= No. of times
8=8 or more times
9= Don't know

4b. Of these ____ times, I will now ask you about the worst time.
During the worst time of high fever....

i.....how many days did the worst time of high fever last?

☐☐

01-97=No. of days
98=98 or more days
99=Don't know

ii.....where or by whom was this child treated?

☐

0=Not treated
1=Home remedy
2=Shaman (Religious Healer)
3=Homeopath/Ayurveda/Kabiraj
4=Medicine shop
5=Village doctor
6=Paramedic (FWV,MA,HA, SACMO, Pharmacist ,SC,FWC,CC, etc.)
7=Doctor(MBBS)/Clinic
8=Hospital(THC)
9=Don't know

iii. ....how old was this child (in completed months)?

☐

3-6=Number of Months
9=Don't know

4c. How many days in the past 7 days has this child had a high fever (hot to touch) ?

☐

0=None
1-7=No. of days
9=Don't know

C

SECTION C: BLEEDING DISEASE

1. At any time in the child's life did he/she have...	A	(If A is yes:) *At what age did this first occur ?* B	(If A is yes) *By whom or where was the child treated for this ?*
	0=No 1=Yes (Go to B) 9=Don't know	001-365=No of days 999=Don't know	0=Not treated 1=Home remedy 2=Shaman (Religious Healer) 3=Homeopath/Ayurveda/Kobiraj 4=Medicine shop 5=Village doctor 6=Paramedic (FWV, MA, HA,SACMO, Pharmacist, SC, FWC,CC, etc.) 7=Doctor (MBBS) / Clinic 8=Hospital (THC) 9=Don't know
a. a nosebleed ?	☐	☐☐☐	☐
b. any bruising on the body ?	☐	☐☐☐	☐
c. a bleeding umbilicus ?	☐	☐☐☐	☐
d. bright red blood in stools ?	☐	☐☐☐	☐
e. very dark stools ?	☐	☐☐☐	☐
f. a bulging fontanelle ?	☐	☐☐☐	☐

Workspace:_____

_____

_____

FI **NOTE: if infant was female, go to Section D.**

2. (If infant was male) Was the infant circumcized ? ☐

0=No (Go to Section D)
1=Yes (Go to 2a)
9=Don't know (Go to Section D)

2a. At what age was the infant circumcized ? ☐☐☐

000-365=No. of days
999=Don't know

Workspace:_____

_____

_____

2b. Did the infant bleed a lot after circumcision ? ☐

0=No (Go to Section D)
1=Yes (Go to 2bi)
9=Don't know (Go to Section D)

C

2bi. From whom or where was treatment sought for this bleeding ?

☐

0=Not treated
1=Home remedy
2=Shaman (Religious Healer)
3=Homeopath / Ayurveda / Kobiraj / Hazam
4=Medicine shop
5=Village doctor
6=Paramedic (FWV, MA, HA,Pharmacist SACMO,SC, FWC,CC)
7=Doctor (MBBS) / Clinic
8=Hospital (THC)
9=Don't know

D

SECTION D: BREASTFEEDING

1. Are you currently breast feeding this child? ☐

0=No (Go to 1a)
1=Yes (Go to 2)
9=Don't know (Go to Section E)

1a. At what age did you stop breast feeding this child? ☐☐☐

001-365 = Age in days
999= Don't Know

Workspace:_____

_____

_____

1b. Why did you stop breastfeeding this child? ☐

1= Mother is ill or weak
2= Child is ill or weak
3= Nipple/Breast Problem
4= Insufficient Milk
5= Mother busy working
6= Child refused
7= Other, Specify_____
9= Don't Know

→ Go to Section D

2. During all of yesterday and night how many times did you breastfeed this child? ☐☐

00= None
01-98= Number of times
99=Don't know

3. Is this child getting enough breast milk, that is, as much as he/she wants? ☐

0=No
1=Yes
9=Don't Know

E

SECTION E : CHILD DIET

1. Does this child presently take any of the following foods/liquids on a regular basis; that is, every day or every other day?	A	If yes, age in months when fed the first time B	If yes, how many times has this child had this food in the past 7 days? C	Did this child eat this food yesterday? D
Food	0=No 1=Yes 9=Don't know	0=< 1 month 1-6= No. of months 9=Don't know	00=None 01-98=No of times 99=Don't know	0=No 1=Yes 9=Don't know
a. Cow, goat, sheep, buffalo, milk	☐	☐	☐☐	☐
b. Powdered milk (Dano, Red Cow, etc...)	☐	☐	☐☐	☐
c. Other mother's milk	☐	☐	☐☐	☐
d. Baby formula (My Boy, Cerelac, etc...)	☐	☐	☐☐	☐
e. Suji	☐	☐	☐☐	☐
f. Payesh	☐	☐	☐☐	☐
g. Wheat or rice flour (gruel)	☐	☐	☐☐	☐
h. Tapioca (Shago/Shoti)	☐	☐	☐☐	☐
i. Rice	☐	☐	☐☐	☐
j. Khichari	☐	☐	☐☐	☐
k. Barley	☐	☐	☐☐	☐
l. Water	☐	☐	☐☐	☐
m. Sweet / Sugar Water	☐	☐	☐☐	☐
n. Ripe Banana	☐	☐	☐☐	☐
o. Milk tea	☐	☐	☐☐	☐
p. Biscuits	☐	☐	☐☐	☐
q. Other, Specify	☐	☐	☐☐	☐
r. Other, Specify	☐	☐	☐☐	☐

SECTION F: CHILD IMMUNIZATION RECORD

F

Note: Ask mother for the infant's vaccine card and examine it.

1. Was this child ever given or fed any vaccinations to prevent him/her from getting diseases (the 6 deadly diseases)? ☐

0=No (Go to Section G)
1=Yes (Go to 1a)
9=Don't know (Go to G)

	A Please tell me if (CHILD NAME) received ..... 0= No 1=Yes 9= Don't Know	B If yes, how many times? 1-8=No. of times 9= Don't Know	C *FI: Check card to confirm vaccine:* 0= Card, no doses 1-8= No. of doses 9= No card
1a. DPT vaccination against diptheria, pertusis and tetanus (injection in the thigh) ?	☐	☐	☐
1b. Polio vaccine (that is, drops in the mouth) ?	☐	☐	☐

SECTION G: CHILD ANTHROPOMETRY

G

1. MUAC : cm		
a. ☐☐.☐	b. ☐☐.☐	c. ☐☐.☐
2. Head circumference : cm		
a. ☐☐.☐	b. ☐☐.☐	c. ☐☐.☐
3. Chest circumference: cm		
a. ☐☐.☐	b. ☐☐.☐	c. ☐☐.☐

66.6=Refused
99.9 Don't know

==========

NOTE: Enter "1" for Form Status on Page 1

Appendix III

JiVitA-1 Infant Verbal Autopsy (IVBA)

Week of Interview: ☐☐☐ Date: ☐☐-☐☐-☐☐ (dd-mm-yy)

Worker ID: ☐☐☐☐ Initials _____

SECTION A: IDENTIFIERS/ADDRESSES

(Note to FI: Confirm name and identifiers of the woman and deceased infant.) A

TL fill out from PTL:

Union : ☐☐☐ Mauza : _____ TL PIN: ☐☐

Sector: ☐☐☐ HH: ☐☐☐☐ Woman's ID: ☐

Name: _____ Husband's Name: _____

CID: ☐ Infant Name: _____ Sex: ☐

1=Male
2=Female
9=Don't know

Relation of respondent to deceased infant:

1. ☐ 2. ☐ 3. ☐

1=Mother
2=Father
3=Grandmother
4=Grandfather
5=Other, specify:_____
9=Don't know

Form Status: ☐

1= Consent given/form completed
2= Not met until the end of the study
6= Refused or consent not given
7= Permanently moved
→ **STOP**

SECTION B: VITAL INFORMATION

(TL: Fill out the following information about the deceased infant from PTL, if available) B

1. Date of birth ☐☐-☐☐-20☐☐ (dd-mm-yy) *99-99-99=Don't know*

2. Date of death ☐☐-☐☐-20☐☐ (dd-mm-yy) *99-99-99=Don't know*

FI Note: If age at death is ≥ 1 year, STOP INTERVIEW. Code "1" in Form Status Box.

3.(FI complete:) Was age at death > 48 hours? ☐

0=No
1=Yes → FI: All gray box questions must be asked.
9=Don't know

B

4. Where did the infant die?

☐☐

01=Parent's home
02=Grandparent's home
03=Neighbors/friends/relatives house
04=FWC
05=THC
06=MCWC
07=District hospital
08=Private clinic
09=Medical college
10=Enroute to or from any health facility
11=Other. Specify _____
99=Don't know

5. Did any "doctor" or health worker of any type visit or treat the infant at the time of death or in the two weeks before his/her death?

☐

0=No (Go to Section C)
1=Yes (Go to 5a)
9=Don't know (Go to Section C)

5a. Type of "doctor" / health worker?	5b. Was he/she present at the time of the infant's death? *0=No* *1=Yes* *9=Don't Know*	5c. Did the "doctor" or health worker tell you why the infant died? *0=No (Go to Section C)* *1=Yes (Go to 5d)* *9=Don't know (Go to Section C)*	5d. (*If 5c is yes*) What were the **reasons** given as to why the infant died? ***(FI: Write verbatim response)***
☐	☐	☐	
☐	☐	☐	
☐	☐	☐	
☐	☐	☐	

Codes for 5a
1=TBA
2=Shaman
3=Homeopath / Ayurvedic
4=Medicine Shop
5=Village doctor
6=Paramedic (FWV, MA, HA, PHARMACIST, SACMO, SC, etc.)
7=MBBS doctor
8=Hospital doctor
9=Don't know

SECTION C: CONDITION AT BIRTH AND FIRST MONTH OF LIFE

I am now going to ask you questions about the condition of your baby at birth and health in the 1st month of life.

1. Was the size of the infant at birth large, average, small, or very small?

☐

1=Large
2=Medium
3=Small
4=Very Small
9=Don't know

2. (FI show picture.) Which picture which is closest to the size of your baby at birth?

☐

Record number 1-4
9=Don't know

3. How many months (running) pregnant were you when you gave birth ?

☐☐

01-11= No. of running months
99= Don't Know

4. How long after birth did the infant begin crying or breathing: within a minute or more than 1 minute?

☐

1=Within a minute
2=More than 1 minute
9=Don't know

5. How was the infant crying right after birth: weakly, normally or vigorously ?

☐

1=Cried weakly / did not cry
2=Cried normally or vigorously
9=Don't know

FI NOTE: If Section B, question 3 is 'YES' (age at death >48 hours):

6. Did the infant stop crying or had a weak or abnormal cry (not loud) from 3-28 days after birth?

☐

0=No
1=Yes
9=Don't know

7. How did the infant move its limbs right after birth: not at all, weakly, normally or vigorously?

☐

0=Did not move
1=Moved weakly
2=Moved normally or vigorously
9=Don't know

FI NOTE: If Section B, question 3 is YES (age at death >48 hours):

8. Did the infant become lethargic, continuously drowsy or unconscious from 3-28 days after birth?

☐

0=No
1=Yes
9=Don't know

9. Was the infant blue all over or did it have blue hands or feet at birth?

☐ 0=No
1=Yes
9=Don't know

10. Did the infant have yellow eyes in the 24 hours following birth?

☐ 0=No
1=Yes
9=Don't know

11. Did the infant choke or froth during feedings given immediately after birth?

☐ 0=No
1=Yes
9=Don't know

12. Did the infant have any convulsion/seizures in the 2 days after birth?

☐ 0=No
1=Yes
9=Don't know

FI NOTE: If Section B, question 3 is YES (age at death >48 hours):
13. Did the infant have any convulsions/seizures in the 3-28 days after birth?

☐ 0=No
1=Yes
9=Don't know

14. Did the infant have high fever (hot to the touch) in the first month of life?

☐ 0=No
1=Yes
9=Don't know

15. Did the infant have a very red umbilicus or discharge from the umbilicus within 28 days after birth?

☐ 0=No
1=Yes
9=Don't know

16. At birth, did the infant have any abnormality or marks ?

0=No abnormality
1=Abnormal
9=Don't know

		Describe Abnormality
a. Head	☐	
b. Eyes	☐	
c. Ears	☐	
d. Nose	☐	
e. Mouth/lips	☐	
f. Jaw	☐	
g. Arms	☐	
h. Hands / fingers	☐	
i. Stomach / Chest	☐	
j. Back	☐	
k. Legs	☐	
l. Feet / toes	☐	
m. Genitals	☐	
n. Buttocks	☐	
o. Skin	☐	
p. Other	☐	

If "Other", describe: _____

SECTION D: INJURY OR VIOLENT EVENT

D

I will now ask you some questions about any injury or accident that might have happened to this infant before his or her death.

1. Did the infant receive an injury/accident/animal bite or experience any other violent event?

☐

0=No (Go to Section E)
1=Yes (Go to 1a)
9=Don't know (Go to Section E)

1a. Describe what happened.

_____

_____

_____

_____

_____

_____

1b. FI: Enter injury or accident type based on the above (question 1a) description:
(If more than one accident or injury is reported, then enter the most recent one.)

☐☐

01= Burning
02= Drowning
03= Fall
04=Motor vehicle accident
05=Other accident
06=Snake (or other animal) bite
07=Poisoning
08=Hand Beating, Kicking
09=Gun shot
10=Cut
11=Blunt Trauma
12=Suffocation
13=Electrocution / Lightning Strike
14=Other
99=Don't Know

1c. Did the infant die from this injury?

☐

0=No
1=Yes
9=Don't know

1d. How long was it between the injury and the infant's death?

Time ☐☐

00-98=Time
99=Don't Know

Units ☐

1=Hours
2=Days
3=Weeks
4=Months

SECTION E: ILLNESS SYMPTOMS

(FI NOTE:** If Section B, question 3 is **NO** (age at death < 48 hours): **Skip to Section F)

I am now going to ask you questions about any health problem your baby had in the 7 days before death.

Respiratory Disease

1. Did the infant have a cough or cold in the 7 days before death?

☐ 0=No (Go to 2)
1=Yes (Go to 1a)
9=Don't know (Go to 2)

1a. How many days did the infant have a cough or cold?

☐ 1-7=No. of days
9=Don't know

1b. Was the cold or cough accompanied by fever?

☐ 0=No (Go to 2)
1=Yes (Go to 1bi)
9=Don't know (Go to 2)

1bi. For how many days did the fever last?

☐ 1-7=No. of days
9=Don't know

2. Did the infant have difficulty breathing in the 7 days before death?

0=No (Go to 3)
1=Yes (Go to 2a)
9=Don't know (Go to 3)

2a. How many days did the infant have difficulty breathing?

☐ 1-7=No. of days
9=Don't know

2b. Was the difficulty breathing accompanied by fever?

☐ 0=No (Go to 3)
1=Yes (Go to 2bi)
9=Don't know (Go to 3)

2bi. If yes, for how many days did the fever last?

☐ 1-7=No. of days
9=Don't know

3. Did the infant breathe faster than normal in the 7 days before death?

☐ 0=No (Go to 4)
1=Yes (Go to 3a)
9=Don't know (Go to 4)

3a. How many days did the infant breath faster than normal?

☐ 1-7=No. of days
9=Don't know

4. Did the infant's nostrils move in and out as he/she breathed in the 7 days before death?

☐ 0=No (Go to 5)
1=Yes (Go to 4a)
9=Don't know (Go to 5)

4a. How many days did the infant's nostrils move in and out as he/she breathed?

☐ 1-7=No. of days
9=Don't know

5. Did the infant make wheezing sounds when breathing in the 7 days before death?

☐ 0=No (Go to 6)
1=Yes (Go to 5a)
9=Don't know (Go to 6)

5a. How many days did the infant make wheezing sounds?

☐ 1-7=No. of days
9=Don't know

6. Did the infant have high pitched whistling in the 7 days before death?

☐ 0=No (Go to 7)
1=Yes (Go to 6a)
9=Don't know (Go to 7)

6a. How many days did the infant have high pitched whistling?

☐ 1-7=No. of days
9=Don't know

7. Did the infant make grunting sounds when breathing in the 7 days before death?

☐ 0=No (Go to 8)
1=Yes (Go to 7a)
9=Don't know (Go to 8)

7a. How many days did the infant make grunting sounds?

☐ 1-7=No. of days
9=Don't know

8. Did the infant have chest indrawing in the 7 days before death?

☐ 0=No (Go to 9)
1=Yes (Go to 8a)
9=Don't know (Go to 9)

8a. How many days did the infant have chest indrawing?

☐
0=No (Go to 9)
1=Yes (Go to 9)
9=Don't know (Go to 9)

9. Did the infant ever stop breathing for a long time and then start again in the 7 days before death?

☐
0=No (Go to 10)
1=Yes (Go to 10)
9=Don't know (Go to 10)

Diarrhea/Dysentery

10. Did the infant have loose, watery stools in the 7 days before death?

☐
0=No (Go to 11)
1=Yes (Go to 10a)
9=Don't know (Go to 11)

10a. How many days did he or she have loose, watery stools?

☐
1-7=No. of days
9=Don't know

10b. What was the highest frequency of loose, watery stools on the worst day?

☐☐
01-30=No. of stools
99=Don't know

10c. Did the infant breastfeed or drink any liquid during the time of loose, watery stools?

☐
0=No
1=Yes
9=Don't know

10d. Was the loose watery stools accompanied by fever?

☐
0=No (Go to 11)
1=Yes (Go to 10di)
9=Don't know (Go to 11)

10di. For how many days did the fever last?

☐
1-7=No. of days
9=Don't know

11. Did the infant have any blood in his/her stools in the 7 days before death?

☐
0=No (Go to 12)
1=Yes (Go to 11a)
9=Don't know (Go to 12)

11a. On how many total days was there blood in the stools?

☐
1-7=No. of days
9=Don't know

12. Did the infant vomit frequently in the two days before death?

☐
0=No
1=Yes
9=Don't know

13. Did the infant stop urinating in the two days before death? ☐

0=No
1=Yes
9=Don't know

Skin Diseases

14 . Did the infant have a rash in the 7 days before death? ☐

0=No (Go to 15)
1=Yes (Go to 14a)
9=Don't know (Go to 15)

14a. Where on the infant's body was the rash?

i. ☐ ii. ☐ iii. ☐

1= Head / Neck
2= Chest / Stomach
3= Back
4= Arms / hands
5= Armpit
6= Buttocks / groin
7= Legs / feet
8= All over
9=Don't know

14b. Was the rash flat or raised? ☐

1=Flat
2=Raised
9=Don't know

14c. Did the rash have blisters containing water or pus? ☐

0=No water or pus
1=Water
2=Pus
9=Don't know

14d. Did the skin crack or peel after the rash? ☐

0=No
1=Yes
9=Don't know

15. Did the infant have "measles"? ☐

0=No
1=Yes
9=Don't know

FI Note: If age at death is < 28 days, SKIP TO SECTION F.

E

Other Conditions

16. Did your infant stop being able to grasp in the 7 days before death?

☐ 0=No (Go to 17)
1=Yes (Go to 16a)
9=Don't know (Go to 17)

16a. How long before your infant died did he/she stop being able to grasp?

☐ 1=Less than 12 hours
2=12 hours or more
9=Don't know

17. Did the infant stop being able to respond to a voice in the 7 days before death?

☐ 0=No (Go to 18)
1=Yes (Go to 17a)
9=Don't know (Go to 18)

17a. How long before he/she died did the infant stop being able to respond to a voice?

☐ 1=Less than 12 hours
2=12 hours or more
9=Don't know

18. Normally, when an object is dangled in front of an infant, the infant follows the movement with its eyes. Did the infant stop being able to follow movements with his/her eyes?

☐ 0=No (Go to Section F)
1=Yes (Go to 18a)
9=Don't know (Go to Section

18a. How long before the infant died did he/she stop being able to follow movements with their eyes?

☐ 1=Less than 12 hours
2=12 hours or more
9=Don't know

F

SECTION F: BLEEDING COMPLICATIONS

1. Did the infant have a bulging fontanelle in the 7 days before death? ☐

0=No
1=Yes
9=Don't know

2. Did the infant ever have…	A	*(If A is yes:)* At what age did this first occur ? B	*(If A is yes) From whom or where did you seek treatment for this ?* C
	0=No 1=Yes (Go to B) 9=Don't know	001-365=No of days 999=Don't know	0=Not treated 1=Home remedy 2=Shaman (Religious Healer) 3=Homeopath/Ayurveda 4=Medicine shop 5=Village doctor 6=Paramedic (FWV, MA, HA,SACMO,Pharmacist SC, FWC,CC, etc.) 7=Doctor (MBBS) / Clinic 8=Hospital (THC) 9=Don't know
a. a nosebleed ?	☐	☐☐☐	☐
b. any bruising on the body ?	☐	☐☐☐	☐
c. a bleeding umbilicus ?	☐	☐☐☐	☐
d. bright red blood in stools ?	☐	☐☐☐	☐
e. very dark stools ?	☐	☐☐☐	☐
f. a bulging fontanelle ?	☐	☐☐☐	☐

FI NOTE: If infant was female, go to Section G.

3. (If infant was male) was the infant circumcized ? ☐

0=No (Go to Section G)
1=Yes (Go to 3a)
9=Don't know (Go to Section G)

3a. At what age was the infant circumcized ? ☐☐☐

001-365=No. of days
999=Don't know

3b. Did the infant bleed a lot after circumcision ? ☐

0=No (Go to Section G)
1=Yes (Go to 3bi)
9=Don't know (Go to Section G)

3bi. From whom or where was treatment sought for this bleeding ? ☐

0=Not treated
1=Home remedy
2=Shaman (Religious Healer)
3=Homeopath/Ayurveda/Hazam
4=Medicine shop
5=Village doctor
6=Paramedic (FWV, MA, HA, SACMO, PHARMACIST,SC, FWC,CC, etc.)
7=Doctor (MBBS) / Clinic
8=Hospital (THC)
9=Don't know

SECTION G: INFANT IMMUNIZATION RECORD

Note: Ask mother for the infant's vaccine card and examine it.

1. Was the infant ever given or fed any vaccinations to prevent him/her from getting diseases (the 6 deadly diseases)? ☐

0=No (Go to Section H)
1=Yes (Go to 2a)
9=Don't know (Go to Section H)

	A	B	C
2.	Please tell me if (INFANT NAME) received a ..... *0= No / Not Applicable 1=Yes 9= Don't know*	If yes, how many times? *1-8=No. of times 9= Don't Know*	FI: Check card to confirm vaccine: *0= Card, no doses 1-3= No. of doses 9= No card*
a. BCG vaccine against tuberculosis, that is an injection in the shoulder that caused a scar ?	☐		☐
b. DPT vaccination against diptheria, pertusis and tetanus, that is an injection in the thigh ?	☐	☐	☐
c. Polio vaccine, that is, drops in the mouth ?	☐	☐	☐
d. Measles vaccine, that is, an injection in the thigh at 9 months of age ?	☐		☐

SECTION H: BREASTFEEDING

I will now ask you some questions about breastfeeding this infant since birth.

1. Did you ever breastfeed the infant ? ☐

0=No (Go to 1a)
1=Yes (Go to 2)
9=Don't know (Go to Section I)

1a. Why did you not breastfeed the infant?

i. ☐ ii. ☐ iii. ☐

1= Mother is ill or weak
2= Infant is ill or weak
3= Nipple/Breast Problem
4= Insufficient Milk
5= Mother busy working
6= Infant refused breast milk
7= Infant died
8= Other, Specify_____
9= Don't Know

→ Go to Section I

2. How many hours after birth did you start to breastfeed the infant? ☐

00= Less than 1 h
01-97=No. of hours
98=98 or more hours
99=Don't know

3. Was the infant able to suckle or breastfeed normally after birth? ☐

0=No
1=Yes
9=Don't know

4. Did you feed the infant colostrum? ☐
0=No (Go to 4a)
1=Yes (Go to 5)
9=Don't know (Go to 5)

4a. What did you do with the colostrum? ☐
1=Discard it
2=Nothing
3=Others, Specify_____
9=Don't Know

5. Had you stopped breastfeeding the infant ? ☐
0=No (Go to 6)
1=Yes (Go to 5a)
9=Don't know (Go to 6)

5a. How many days after birth had you stopped breastfeeding the infant? ☐☐☐
000=Less than 1 day
001-365= No of days after birth
999= Don't Know

5b. How many days before death had you stopped breastfeeding the infant? ☐☐☐
000=Less than 1 day
001-365= No of days before death
999= Don't Know

5c. Why had you stopped breastfeeding? ☐
1= Mother was ill or weak
2= Infant was ill or weak
3= Nipple/Breast Problem
4= Insufficient Milk
5= Mother busy working
6= Infant refused breast milk
7= Breast milk not needed
8= Other, Specify_____
9= Don't Know

6. Before death, did the infant stop suckling or feeding in a normal way? ☐
0=No (Go to Section I)
1=Yes (Go to 6a)
9=Don't know (Go to Section I)

6a. How many days before death did the infant stop suckling or feeding in a normal way? ☐
1=Less than one day
2=One to two days
3=Three to seven days
4=Eight to 14 days
5=15 to 30 days
6=31 or more days
9=Don't know

SECTION I: INFANT DIET

I am now going to ask you some questions about this infant's diet since birth.

1. Was anything, other than the mother's breast milk offered to the infant within 3 days after birth? ☐
0=No (Go to Section J)
1=Yes (Go to 1a)
9=Don't know / Not applicable (Go to Section J)

1a. What was offered? A ☐ B ☐ C ☐

1=Cow/goat/sheep/buffalo milk
2=Water
3=Powdered milk
4=Honey
5=Other mother's milk
6=Sugar water / Misri Water
7=Oil
8=Other (Specify:_____)
9=Don't know

1b. Was the infant given ..... since birth?	A	If yes, age in days when fed the first time. B
Food	0=No 1=Yes (Go to B) 9=Don't know	001-364=No of days 999=Don't know
i. Cow, goat, sheep buffalo, milk	☐ →	☐☐☐
ii. Powdered milk (Dano, Red Cow, Anchor, "Freshmilk" etc...)	☐ →	☐☐☐
iii. Other mother's milk	☐ →	☐☐☐
iv. Baby formula (My Boy, Cerelac, Lactogen etc.)	☐ →	☐☐☐
v. Suji	☐ →	☐☐☐
vi. Payesh	☐ →	☐☐☐
vii. Wheat or rice flour (gruel)	☐ →	☐☐☐
viii. Tapioca (Shago/Shoti)	☐ →	☐☐☐
ix. Rice	☐ →	☐☐☐
x. Khichuri	☐ →	☐☐☐
xi. Barley	☐ →	☐☐☐
xii. Water	☐ →	☐☐☐
xiii. Sweetened / Sugar Water	☐ →	☐☐☐
xiv. Ripe Banana	☐ →	☐☐☐
xv. Milk tea	☐ →	☐☐☐
xvi. Biscuits	☐ →	☐☐☐
xvii. Other Specify_____	☐ →	☐☐☐
xviii. Other Specify_____	☐ →	☐☐☐

SECTION J: NARRATIVE HISTORY

Please tell me all the details of how the infant died.

Appendix IV

Operational Definitions

Nasal Bleeding:

Any bleeding from inside of nose considered as nasal bleeding. Any bleeding from cut of the upper part of nose was not considered. Continuous flow of nasal bleeding (like molasses) was also recorded as nasal bleeding. Any nasal bleeding after death was not recorded.

Bruising:

Any occurring of blue/black spot like ecchymosis was considered as bruising. Interviewers probed to exclude any birth mark and marks due to ulcer, burn, itching. If the bruising was due to birthing process the interviewers considered that as bruising.

No red mark was considered as bruising.

If bruising developed after death it was not recorded

Umbilical Bleeding:

Any umbilical bleeding occurred after knotting the cord. Bleeding during cutting or knotting the cord was not recorded. Pus discharge or any other discharge not considered as umbilical bleeding. Umbilical bleeding after death was not recorded.

Red Blood in Stool (Fresh Intestinal Bleeding):

Any occurring of fresh red blood in stool with or without dysentery considered as red blood in stool. Interviewers probed for red blood in stool. Red blood in stool after death were not recorded

Dark Stool:

Any reporting of black tarry stools were recorded as dark stool, meconium (Interviewers probed the respondents to exclude first greenish/black stool as dark stool) was excluded as dark stool) Dark stool after death was not recorded.

Bulging Fontanel:

Maternal reporting of bulged fontanel was recorded. Local term "brammo talu" was used.

Bleeding during Circumcision:

Any reporting of excessive bleeding after circumcision was recorded. Bleeding during circumcision was not considered.

Time of First Episodes:

If any of the above bleeding occurred to the infants then the interviewers asked the respondents; at what age did this first occur? Time was then recorded in days.

Deceased Infants

Infants who died by 6 months of age

Surviving Infants

Infants who survived up to six months of age

Bleeding Status and Interventions of JiVitA Trials

In this appendix, bleeding status of infants was analyzed with the different intervention codes used in the two JiVitA trials in which data collection of the index study was nested. The objective of this analysis was to see whether there was any difference in bleeding status of infants by interventions used in the two trials. In the maternal trial the intervention groups were Vitamin A (~23,000 IU), Beta-carotene (42 mg) and the comparison group was placebo. In the subsequent infant trial, babies born to enrolled mothers of JiVitA-1 trial of each intervention arm were randomly assigned to either Vitamin A (~50,000 IU) or placebo. Mothers who were tested positive for pregnancy and consented to participate in the JiVitA-1 trial were dosed weekly throughout pregnancy up to 3 months post partum. Enrolled babies in JiVitA -2 trials were dosed once either with vitamin A or placebo at birth (Annexure I). As the main results of the trials were yet to be published, the codes were not revealed for this analysis.

12.1 Any Bleeding Status by Infants' Intervention Codes

When analyzed, any bleeding status of infants with infants' interventions used in JiVitA trial, similar percentages of bleeding status were found for code A (50.2%) and code B (49.8%).

Table 12.1: Distribution of bleeding status by infants' intervention Codes

Infants' Intervention Code	**Infants who had bleeding** n=1573		**Infants who did not have bleeding** n=15336	
	No.	%	No.	%
A	789	50.2	7633	49.8
B	784	49.8	7703	50.2
Pearsons $Chi^2(1)=0.0855$				*p=0.770*

The percentage distributions were also found very similar for infants who had bleeding and who did not have bleeding for both codes A (50.2% and 49.8%) and code B (49.8% and 50.2%). There were no statistical differences in bleeding status of infants for the trial interventions (p=0.770).

12.2 Any Bleeding Status by Mothers' Interventions for Infants' Intervention Code "A"

When analyzed for any bleeding status by maternal intervention codes X, Y and Z for infants' intervention code "A", similar distributions were found for infants who had bleeding and who did not have bleeding in all the maternal intervention codes as in X (35.5% and 34.1%), in Y (34.1% and 33.5%) and in Z (30.4% and 32.4), respectively. The differences were not statistically significant (p=0.526).

Table 12.2: Distribution of bleeding status by mothers' intervention for infants' intervention code "A"

Maternal Intervention Code	**Infants who had bleeding** n=789		**Infants who did not have bleeding** n=7633	
	No.	%	No.	%
X	280	35.5	2604	34.1
Y	269	34.1	2560	33.5
Z	240	30.4	2469	32.4
Pearsons Chi2(2)=1.2857			*p=0.526*	

12.3 Any Bleeding Status by Mothers' Interventions for Infants' Intervention Code "B"

When analyzed for any bleeding status by maternal interventions codes X, Y and Z for infants' intervention code "B", similar distributions were found for infants who had bleeding and those who did not have bleeding in all the maternal intervention codes as in X (32.4% and 32.6%), in Y (36.1% and 33.3%) and in Z (31.5% and 34.1), respectively. The differences were not statistically significant (p=0.213).

Table 12.3: Distribution of bleeding status by mothers' intervention for infants' intervention code "B"

Maternal Intervention Code	**Infants who had bleeding** n=784		**Infants who did not have bleeding** n=7703	
	No.	%	No.	%
X	254	32.4	2513	32.6
Y	283	36.1	2564	33.3
Z	247	31.5	2626	34.1
Pearsons Chi^2 (2)=3.0927			*p=0.213*	

12.4 Any Nasal Bleeding or Bulging Fontanel Status by Infants' Intervention Codes

When analyzed for either nasal bleeding or bulging fontanel status of infants with infants' intervention codes, similar percentages of bleeding status were found for code A (50.8%) and code B (49.2%).

Table 12.4: Distribution of any nasal bleeding or bulging fontanel status by infants' intervention codes

Infants' Intervention Code	**Infants who had nasal bleeding or bulging fontanel** n=386		**Infants who did not have bleeding** n=16523	
	No.	%	No.	%
A	196	50.8	8226	49.8
B	190	49.2	8297	50.2
Pearsons Chi^2 (1)=0.1485			*p=0.700*	

The percentage distributions were also very similar for infants who had bleeding and who did not have bleeding for both code A (50.8% and 49.8%) and code B (49.2% and 50.2%), respectively. The differences were not statistically significant (p=0.770).

12.5 Any nasal bleeding or bulging fontanel status by mothers' interventions for infants' intervention code "A"

When analyzed for any nasal bleeding or bulging fontanel status by maternal interventions codes X, Y and Z for infants' intervention code "A", similar distributions were found for infants who had bleeding and who did not have bleeding in all the maternal codes as in X (29.6% and 34.4%), in Y (37.2% and 33.5%) and in Z (33.2% and 32.1), respectively. The differences were not statistically significant (p=0.345).

Table 12.5: Distribution of any nasal bleeding or bulging fontanel status by mothers' interventions for infants intervention code "A"

Maternal Intervention Code	**Infants who had nasal bleeding or bulging fontanel** n=196		**Infants who did not have bleeding** n=8226	
	No.	%	No.	%
X	58	29.6	2826	34.4
Y	73	37.2	2756	33.5
Z	65	33.2	2644	32.1
Pearsons $Chi^2(2)=2.1279$			*p=0.345*	

The percentage distributions were also very similar for infants who had bleeding and who did not have bleeding for both code A (50.8% and 49.8%) and code B (49.2% and 50.2%), respectively. The differences were not statistically significant (p=0.770).

12.5 Any nasal bleeding or bulging fontanel status by mothers' interventions for infants' intervention code "A"

When analyzed for any nasal bleeding or bulging fontanel status by maternal interventions codes X, Y and Z for infants' intervention code "A", similar distributions were found for infants who had bleeding and who did not have bleeding in all the maternal codes as in X (29.6% and 34.4%), in Y (37.2% and 33.5%) and in Z (33.2% and 32.1), respectively. The differences were not statistically significant (p=0.345).

Table 12.5: Distribution of any nasal bleeding or bulging fontanel status by mothers' interventions for infants intervention code "A"

Maternal Intervention Code	**Infants who had nasal bleeding or bulging fontanel** n=196		**Infants who did not have bleeding** n=8226	
	No.	%	No.	%
X	58	29.6	2826	34.4
Y	73	37.2	2756	33.5
Z	65	33.2	2644	32.1
Pearsons $Chi^2(2)=2.1279$			*p=0.345*	

12.6 Any Nasal Bleeding or Bulging Fontanel Status by Mothers' Interventions for Infants' Intervention Code "B"

When analyzed for any nasal bleeding or bulging fontanel status by maternal interventions codes X, Y and Z for infants intervention code "B", similar distributions were found infants who had bleeding and who did not have bleeding in all the maternal codes as in X (36.2% and 32.5%), in Y (35.3% and 33.5%) and in Z (28.4% and 33.9). The differences were not statistically significant (p=0.261).

Table 12.6: Distribution of nasal bleeding or bulging fontanel status by mothers interventions in infants intervention code "B"

Maternal Intervention Code	**Infants who had nasal bleeding or bulging fontanel** n=190		**Infants who did not have bleeding** n=8297	
	No.	%	No.	%
X	69	36.2	2698	32.5
Y	67	35.3	2780	33.5
Z	54	28.4	2819	33.9
Pearsons Chi^2 (2)=2.6860			*p=0.261*	

12.7 Any Nasal Bleeding, Bruising or Umbilical Bleeding Status by Infants' Intervention Codes

When analyzed for any nasal bleeding or bruising or umbilical bleeding status of infants by infants' intervention codes, similar percentages of bleeding status were found for codc A (50.6%) and code B (49.4%). The percentage distributions were also very similar for infants who had bleeding and who did not have bleeding for both code A (50.6% and 49.8%) and code B (49.4% and 50.2%), respectively. The difference was not statistically significant (p=0.642).

Table 12.7: Distribution of any nasal bleeding or bruising or umbilical bleeding status by infants intervention codes

Infants' Intervention Code	**Infants who had nasal bleeding or bruising or umbilical Bleeding** n=870		**Infants who did not have bleeding** n=16039	
	No.	%	No.	%
A	440	50.6	7982	49.8
B	430	49.4	8057	50.2
Pearsons Chi^2 (1)=0.2158			*p=0.642*	

12.8 Any Nasal Bleeding, Bruising or Umbilical Bleeding Status by Mothers' Interventions for Infants' Intervention Code "A"

When analyzed for any nasal bleeding, bruising or umbilical bleeding status by maternal interventions codes X, Y and Z for infants' intervention code "A", similar distributions of infants who had bleeding and who did not have bleeding for all the maternal intervention codes were found as in X (38.4% and 34.0%), in Y (32.5% and 33.7%) and in Z (29.1% and 32.3). The differences were not statistically significant (p=0.144).

Table 12.8: Distribution of nasal bleeding or bruising or umbilical bleeding status by mothers' interventions for infants' intervention code "A"

Maternal Intervention Code	**Infants who had nasal bleeding or bruising or umbilical bleeding** n=440		**Infants who did not have bleeding** n=7982	
	No.	%	No.	%
X	164	38.4	2715	34.0
Y	143	32.5	2686	33.7
Z	128	29.1	2581	32.3
Pearsons Chi^2 (2)=3.8813			*p=0.144*	

12.9 Any Nasal Bleeding, Bruising or Umbilical Bleeding Status by Mothers' Interventions for Infants' Intervention Code "B"

When analyzed any nasal bleeding or bruising or umbilical bleeding status by maternal interventions codes X, Y and Z for infants' intervention code "B", similar distributions of infants who had bleeding and who did not have bleeding in all the maternal codes were found as in X (32.6% and 32.6%), in Y (37.7% and 33.3%) and in Z (29.8% and 34.1%), respectively. The differences were not statistically significant (p=0.104).

Table 12.9: Distribution of any nasal bleeding or bruising or umbilical bleeding status by mothers' intervention for infants' intervention code "B"

Maternal Intervention Code	**Infants who had nasal bleeding or bruising or umbilical bleeding** n=430		**Infants who did not have bleeding** n=8057	
	No.	%	No.	%
X	140	32.6	2627	32.6
Y	162	37.7	2685	33.3
Z	128	29.8	2745	34.1
Pearsons Chi^2 (2)=4.5344			*p=0.104*	

12.10 Summary Findings

In this appendix, analyses of bleeding status of infants with different intervention codes used in the two trials in which data collection of the index study was nested are presented. The objective of the analysis was to see whether there was any differentiation of bleeding status of infants by different interventions used in the maternal and infants' trials. As the main results of the trials have not been published till the writing of this work, the codes were not opened for this analysis. The findings suggest that percentages of infants who had bleeding and who did not have bleeding were similar in different intervention codes for both mothers and infants, and the differences were not statistically significant.