REVIEW OF LITERATURE
Haemorrhagic disease of the newborn (HDN) is a serious haemorrhagic disorder associated with vitamin 'K' deficiency, most commonly seen in breast fed babies.

The term haemorrhagic disease of newborn was first used in 1994 when Townsend reported 50 cases (infants) of bleeding disorder in whom the bleeding had occurred within the first two weeks of life. He observed that the haemorrhage generally began on the 2nd or 3rd day of postnatal life. He also differentiated this acquired haemorrhagic disease from inherited haemophilia.

Vitamin 'K' was not discovered until 1929 when Dam observed bleeding in chickens, fed on fat free diet (Diet free from ether soluble components). Thus "historically, vitamin 'K' (Koagulation vitamin) acquired its name with the discovery that chickens fed on fat free diet bled to death". Since then vitamin 'K' has been isolated in 3-main forms.

Vitamin 'K' is a naphthoquinone derivative and is related to 2-methyl-1, 4-naphthoquinone.

1. First form is vitamin 'K₁': It is a naturally occurring fat soluble, vitamin 'K' found in dark green leafy vegetables, such as spinach, cabbage etc. It possesses phytol radical at position 3. Vitamin
K_1 is also termed as phytonadione or phylloquinone or mephyton.

Vitamin 'K_1': Phytonadione (Phylloquinone; Mephityon).  
(2-methyl-3 phytyl-1, 4-naphthoquinone).

2. Second form is vitamin 'K_2': It is synthesized by intestinal bacterial flora. It has difarnesyl radical at position 3. Vitamin K_2 is also termed as farnoquinone or Menaquinone.

Vitamin K_2: Farnoquinone; Menaquinone  
(2-methyl-3-difarnesyl-1, 4-naphthoquinone).

3. Third form is vitamin 'K_3': It is a synthetic form and water soluble. It is termed as Menadione. It is round in two main forms. First form has a phosphate radical in it and is known as synkayvite. The second form has a sulfate radical in place of phosphate radical and is known as hykinone.
Synkayvite (sodium menadione diphosphate).

Hykinone (Menadione - sodium disulfite).

MERITS AND DEMERITS OF VARIOUS FORMS OF VITAMIN 'K'

1. Naturally occurring vitamin K i.e. vitamin $K_1$ causes hyperbilirubinaemia in premature and compromised infants.

2. Synthetic preparations of vitamin K i.e. vitamin $K_3$ causes hyperbilirubinaemia to a lesser extent than vitamin $K_1$; but it causes hyperbilirubinaemia in those infants who are deficient in G-6 phosphate dehydrogenase enzyme.

3. It has been postulated that synthetic preparation of vitamin 'K$_1$' (konakionone) which can be used orally or parenterally does not cause hyperbilirubinemia of any significance even in G-6 phosphate dehydrogenase deficient infants and, thus, it may be recommended by both routes in doses of 1 mg.
SOURCES AND ABSORPTION OF VITAMIN 'K' IN INFANCY

Sanford et al (1932) observed that diet was an important source of vitamin 'K' immediately after birth. They further suggested that early supplemental feedings could reduce the incidence of haemorrhage during the first week of life.

Aballi et al (1966) claimed that absorption of vitamin 'K' from the colon of human neonate was good but the relative importance of intestinal flora in providing vitamin 'K' to the infant was unknown.

Frick et al (1967) observed, in their study of 10 adults, that total starvation combined with antibiotic administration did not induce vitamin 'K' deficiency until 21 to 28 days had elapsed.

Shearer et al (1970) documented that in a vitamin 'K' replete man the radio activity persisted in the plasma for 3-4 days after the ingestion of tritiated vitamin 'K₁'.

Keenan et al (1971) documented that flora of breast fed infants could produce less vitamin 'K' than the flora or formula fed infants.

Many bacteria, including normal intestinal flora, are capable of synthesizing quinones with vitamin 'K' activity. Cow's milk has more vitamin 'K' than human milk. According to Harper (1977) deficiency of vitamin 'K₂' occurs as a result of prolonged therapy
with sulfaguanidine, succinyl sulfathiazole or salicylate, all capable of suppressive bacterial flora which synthesize vitamin \( \text{K}_2 \).

Bjornsson et al (1980) observed that vitamin K storage in human infant was not known but higher molecular weight storage forms of vitamin K could exist.

Corrigan (1981) observed that fat soluble vitamin \( \text{K}_1 \) or phylloquinone was the principal form of vitamin \( \text{K} \) in plants and vegetable oils and required bile acids for its absorption from small intestine. Author also documented that the vitamin \( \text{K} \) was not stored in human infants to any significant degree. But according to Hollander (1981) in animals the absorption of vitamin \( \text{K}_1 \) across the intestinal mucosa was energy dependent transport.

According to Harron et al (1982), most of the commercial formulae in the United States contain more than 50 micro gm/l of vitamin \( \text{K}_1 \). In contrast, vitamin K content in human milk varies widely, but was generally \( \leq 20 \) micro gm/l and often below 5 micro gm/l.

Bentley and Meganathan (1982) documented that vitamin \( \text{K} \) was synthesized by intestinal mucosa in the form of fat soluble menaquinone or vitamin \( \text{K}_2 \). Authors further documented that the bacteria differed widely in this in their ability to synthesize vitamin \( \text{K}_2 \). Bacteroids fragilis and some strains of E. Coli were
efficient producers of vitamin K\textsubscript{2}, whereas some lactobacilli and pseudomonas organisms were incapable of its synthesis.

Sann et al (1983) observed that oral administration of vitamin K\textsubscript{1} was effective in maintaining significant serum level of vitamin 'K' for at least 5 days.

According to Barness (1987) naturally occurring vitamin 'K' is fat soluble and is found in high concentration in hog's liver, soybeans and alfalfa and in smaller amounts in some vegetables such as spinach, tomatoes, Kale etc. This vitamin was labelled vitamin K\textsubscript{1} to distinguish it from synthetic naphthoquinones with vitamin K like activity.

**BIOLOGIC FUNCTIONS OF VITAMIN 'K'**

Stenflo et al (1974) wrote"the specific action of vitamin K was post-translational carboxylation of glutamic acid residues on (unless it is quoted) vitamin K dependent proteins". This conversion of glutamic acid to Y carboxyglutamic acid creates effective calcium binding sites on these proteins. Noncarboxylated proteins are functionally defective because they cannot bind calcium e.g. prothrombin requires calcium for its activation to thrombin, which in turn converts fibrinogen to fibrin.
Corrigan (1981) observed that oxidative phosphorylation of glutamic acid was due to vitamin K. Synthesis of factor II, factor VII, Factor IX and factor X were dependent on vitamin 'K'. Author further suggested that protein C was vitamin K dependent and when activated inhibited coagulation function of factor VIII and factor V and stimulated fibrinolysis. Author also reported that vitamin K dependent calcium binding proteins such as osteocalcin promoted phospholipid interaction in coagulation and in calcium binding metabolism.


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\text{Peptide-glutamic acid} \xrightarrow{\text{Carboxylation}} \text{Y-carboxyglutamic acid-peptide}
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\[
\text{Vit. K. Hydroxyquinone} \xrightarrow{\text{Vit. K. epoxide}} \text{Vitamin K}
\]

\[
\text{NAD (P) H.} \xrightarrow{\text{Warfarin}} \text{NAD (P) H.}
\]

Courtsey - Gallop et al, Uotilla and Sittie, and Leibman et al.

Vitamin K : Hydroxyquinone - active form of vit. K.
EFFECT OF EXCESS OF VITAMIN 'K' IN NEWBORNS

Barness (1987) documented that effects of excess vitamin K were still not established and claimed that it could produce hyperbilirubinaemia in premature newborn infants if given in higher doses.

MORTALITY AND MORBIDITY OF VITAMIN 'K' DEFICIENCY / HAEMORRHAGE(S)

Dam (1894) reported 50 cases of bleeding which occurred during the first 2 weeks of life, and differentiated it from inherited hemophilia. Stuart (1977) in his study observed that the transient deficiency of vitamin K dependent factors was probably due to lack of free vitamin K in mothers, immaturity of infant's liver and the absence of intestinal bacterial flora (normally responsible for the synthesis of vitamin K). Author further observed that rarely, among the term infants and more frequently among premature infants, there was an accentuation and prolongation of this deficiency between the 2nd and 5th days of life, resulting in spontaneous and prolonged bleeding.

Nakayama et al (1981) reported 425 infants of bleeding disorder due to late onset of vitamin K deficiency.

McNinch et al (1983) reported six cases (6 in 1200 live births) of haemorrhagic disease in a single district, in his 17 month's study period. But, those
at birth.

Martin et al (1983) reported 741 cases of vitamin K deficiency haemorrhage in Vietnam. These cases also included 171 deaths which were traced to the use of warfarin contaminated milk powder.

Lane et al (1983) reported a fatal case of vitamin K deficiency in an otherwise healthy 1-month old child who had not received vitamin K prophylaxis at birth.

Chaou et al (1984) reported intracranial haemorrhage, proved by CT scan, in 32 breast fed babies and traced the relation of their disorder to reduced availability of vitamin K. Further, in a 2 year follow up study of the same, they reported that only one showed normal development while all others developed microcephaly and some degree of handicap.

Sutor et al (1985) from West Germany reported 20 cases over a period of 4 years, suggesting an incidence of 1 per 100,000.

Motohara et al (1987) documented that the level of acarboxyprothrombin (PIVKA-II) was higher in breast fed babies than formula fed babies.

Lane et al (1985) documented that haemorrhagic disease of the newborn (HDN) had an approximate incidence of 1 per 1000 live births.
CLINICAL MANIFESTATIONS OF VITAMIN 'K' DEFICIENCY

Three patterns of haemorrhagic disease of newborn occur in infancy; viz. early-HDN, classic-HDN and late-HDN.

Early HDN:

These infants have severe and often life-threatening haemorrhage at the time of delivery or during the first 24 hours after birth.

Although idiopathic cases have been reported (Anthony, 1961 and Wilson, 1972), the early-HDN is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism. Maternal anticonvulsants have also been linked to early-HDN (Mountain et al, 1970; Bleyer, Skinner, 1976; Deblay et al, 1982 and McNinch et al, 1983).

Early-HDN is seen in those cases whose mothers use therapeutic doses of warfarin (an anticoagulant) during pregnancy (Stevenson et al, 1980).


Classic-HDN

Classic-HDN typically occurs at 2 to 5 days

Sutherland et al (1967) reported that the incidence of classic-HDN prior to the initiation of routine vitamin K prophylaxis varied widely but observed that it could be as high as 1.7% in full term infants. Authors further reported that the incidence of moderate to severe bleeding among breast fed infants, who had not received vitamin K was 15 to 20 times higher than in those who had received cows milk or vitamin 'K' or both.

McNinch et al (1983) observed that affected children developed generalized ecchymoses or gastrointestinal tract bleeding. They documented that intracranial haemorrhage was less common in classic-HDN.

Late-HDN

Haemorrhage occurring one week after postnatal life is considered as late-HDN.

Rapaport (1946) reported 7 infants of hypoprothrombinemia secondary to chronic diarrhoea.

Matsusaka et al (1981) observed that most of the late-HDN infants had acute intracranial haemorrhage which could be intracerebral, intracerebellar, subarachnoid, subdural or epidural. They further documented that many of these infants died, and those who survived frequently had severe neurologic sequelae. Vitamin K deficiency was the leading cause of haemorrhage in
infants, after the first week of life.

Nagi et al (1982) reported that the second most common feature of late haemorrhagic disease was widespread deep ecchymoses or nodular purpura.

**VIEWS REGARDING PARENTERAL OR ORAL SUPPLEMENTATION OF VITAMIN K**

Brinkhouske et al (1937) documented low prothrombin levels in normal newborn infants. Others viz. Waddell et al and Nygaard et al (1939) demonstrated that these low levels could be elevated by the administration of vitamin K.

Dam et al (1937) differentiated haemorrhagic disease of the newborn from bleeding, secondary to other causes.

Holt and McIntosh (1939) recommended that all the infants should be promptly given 0.5 mg vitamin K₁ orally at birth.

Aballi et al (1957; 1959) studied coagulation factors in newborns and observed that factor II, VII, IX and X were reduced in the newborns as compared to levels in adults.

The nutrition committee of the American Academy of Pediatrics recommended in 1961, that prophylactic administration of vitamin 'K' be given to all newborn infants.
Aballi and de Lamerens (1962) differentiated haemorrhagic disease of the newborn from bleeding, secondary to other causes.

Welfering (1962) observed that coagulation factors II, VII, IX and X were reduced in newborns as indicated by Thrombotest. He concluded that the test was abnormal when any one or all factors mentioned above were reduced. He opined that in some newborn infants, coagulation deficiency at birth was so great as to constitute a risk of haemorrhage, which could be prevented by administering vitamin 'K' to the mothers 4-24 hours prior to delivery. However, some infants did not show much lowering of coagulability and therefore haemorrhage could be prevented by giving vitamin 'K' orally or parenterally (I/M) just after birth.

Godman and Deposito (1966) reported five patients with bleeding disorder with hypoprothrombinaemia that occurred after neonatal period.

Mountain et al (1970) suggested that anticonvulsant therapy during pregnancy, especially treatment with barbiturates, caused coagulation defects. They suggested that if vitamin 'K' (especially \( K_1 \)) was given to mother near term then there would be no bleeding tendencies in her newborn infant.

Bleyer et al (1976) documented that anticonvulsant therapy during pregnancy i.e. phenobarbitone and
phenytoin sodium caused coagulation defects which could result in bleeding during the early neonatal period.

Van Doorm et al (1977) claimed that haemorrhagic disease of the newborn was due to vitamin 'K' deficiency and developed at 2-4 days of post-natal life. Authors suggested that if haemorrhagic disease of newborn could be prevented by administration of vitamin 'K' then generalised bleeding tendencies in the newborns should be uncommon. Authors also suggested that substitution therapy should be given to high risk infants. They also suggested that it would be a backward step to stop routine prophylaxis with vitamin K.

Hope et al (1982) in their study on three cases of alpha-1-antitrypsin deficiency observed haemorrhagic tendency in them which responded to vitamin K. In their study they stressed that the patients were all breast fed and none had received vitamin K at birth. Because of their presentation with bleeding disorder, they were all initially diagnosed as having haemorrhagic disease of newborn. However, their presentation was not of classical type of neonatal haemorrhage. All of them had conjugated hyperbilirubinaemia in the first few months of life associated with raised transaminase (consistent with neonatal hepatitis) and the clotting disorder was due to lack of vitamin K dependent factors. Authors opined that greater awareness of early features of haemorrhagic disease
of newborn may lead to early diagnosis of the condition. They also suggested that PI(protease inhibitor) pheno-
typing should always be considered in cases of haemorr-
hagic disease in early life, especially if associated
with raised hepatic enzymes.

Vimenez et al (1982) observed that in one month
old infants vitamin K dependent clotting factors, proth-
rombin time (PT) and partial thromboplastin time (PTT)
were similar whether they were breast or bottle fed.
However, the Normotest (NT) and Thrombotest (TT) were
slightly prolonged in breast fed group. They observed
that these values were also higher in breast fed infants
as compared to the adult values. They stressed that the
higher values could be associated with infection, espe-
cially diarrhoea and following antibiotic therapy.

Debley et al (1982) documented that if vitamin
K₁ 20 mg was given orally daily for two days to a mother,
taking antiepileptic drugs, then transplacental transpor-
tation of vitamin K occurred and prevented bleeding
tendencies in the newborn. They suggested that vitamin
K₁ prophylaxis should be a routine for epileptic mothers
near term.

Dunn (1982) stressed that there is a need to
accept the wise consel given by Holt and McIntosh in
1939 that all infants should be promptly given 0.5 mg of
vitamin K₁ orally at birth. He documented that as all
paediatricians appreciate, vitamin $K_1$ was well and rapidly absorbed when given orally. There was, however, a need for the commercial availability of vitamin $K_1$ Powders of 0.5-1.0 mg strength to avoid the expensive practice of using sterile ampoules for oral use. He stressed that the widespread demand of such preparation should make its marketing profitable.

Shirahata et al (1982) noted that 7-10 days after the intramuscular injection of vitamin K coagulation values declined in breast fed infants. But they were unable to determine the normal dose and proportion of its absorption from the gut.

McNinch et al (1983) observed that if vitamin K prophylactically was not given to breast fed babies the problem of haemorrhagic disease of newborn (HDN) became more common. This problem of HDN could prove fatal if not recognised and treated promptly. They also suggested that selective policy of giving vitamin $K_1$ prophylactically only to babies, considered at risk was no longer adequate and that vitamin $K_1$ should be given to every newborn baby.

Verity et al (1983) treated four infants of intracranial haemorrhage secondary to vitamin K deficiency. Three of these infants were noted to have received 1 mg vitamin K at birth. They studied the blood clotting abnormalities and found highly raised prothrombin
time, activated partial thromboplastin time (APTT) and thrombin time (TT). They noted that these abnormal clotting tests reversed to normal, after administering a further dose of vitamin K. They found that these abnormalities were due to deficiency of vitamin K and therefore, concluded that more than 1 mg of vitamin K₁ should be given at the time of birth.

Ware and Mills (1983) suggested that vitamin K should probably be given to all newborn babies and certainly to those who would receive breast feeding.

McKenna et al (1983) studied the effects of warfarin sodium (an anticoagulant) taken by lactating mothers. They claimed that despite easily detectable warfarin values in the plasma of these mothers, none could be identified in their milk. They observed that infants born to these mothers had prolonged prothrombin time but not as long as those mothers themselves: although, warfarin per se was not detected in the plasma of infants. Recommendation by the authors was that mothers receiving warfarin sodium be allowed to breast feed their infants. Authors, however, cautioned that there was a need to establish similar information with regard to other infrequently administered anticoagulants.

Lane et al (1983) opined that a decision to withhold vitamin K prophylaxis was ill advised. They suggested that clinicians should remain alert to the possibility of vitamin K deficient haemorrhage in older
Chaou et al (1984) observed that the prophylactic injection of vitamin K at the time of birth was not a routine procedure in Taiwan. Authors had not seen delayed haemorrhage in any baby born at their hospital.

Nagao and Nakayama (1984) commented on a case report of Lane et al (1983), regarding intracranial haemorrhage in a normal infant who had vitamin K deficiency. Lane et al (1983) had argued against the tendency to stop routine prophylaxis of vitamin K at birth. Authors, while supporting the opinion of routine prophylaxis felt that cases of intracranial haemorrhage (due to idiopathic vitamin K deficiency) found in Japan could be related to the abandonment of routine vitamin K administration at birth. Authors suggest that vitamin K given at birth may not resolve all the problem of idiopathic vitamin K deficiency, but most of it could be prevented.

Aballi (1985) observed that alpha-1 antitrypsin deficiency could actually resulted in inadequate vitamin K absorption consequently low vitamin K in breast milk was unable to compensate for the defective absorption if it was there owing to cholestatic liver disease, alpha-1-antitrypsin deficiency or antibiotic therapy.
Lane et al (1985) observed that exclusively breast fed babies had prolonged prothrombin time and a 15-20 times greater risk of bleeding as compared to those who were given cow's milk or vitamin 'K' or both.

Kries et al (1985) observed that in late onset of HDPN some other factors must be involved. One possibility was malabsorption of vitamin K, perhaps due to intraluminal bile salt deficiency.

Motohara et al (1985) suggested that PIVKA-II level might be more useful than a coagulation test, since low activity of vitamin K dependent coagulation factors some time reflect impaired production of these factors (due to immaturity rather than vitamin K deficiency. The level of PIVKA-II (protein, induced by vitamin K absence) or antagonistic II was raised in the state of vitamin K deficiency and was normal after administration of vitamin K. Authors depicted the mechanism of PIVKA-II as follows:

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\text{PIVKA-II} \xrightarrow{\text{Vitamin K}} \text{Prothrombin} \\
\text{(Prothrombin Precursor)}
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Authors observed that lack of data on PIVKA-II levels in cord blood in newborn was the cause of vitamin K prophylaxis controversy. The level of PIVKA-II was measured by ELISA technique using a monoclonal antibody.

According to McNinch et al (1985) vitamin K does not cross the placenta easily. Its concentration
maternal value and the mean concentration of vitamin K dependent factors (II, VII, IX and X) were only 30-60% of the normal adult values. 500 ml breast milk contains 0.5 - 3 ugm vitamin K₁ while 500 ml of bottle feed would yield approximately 1.5 - 4.5 ugm of vitamin K₁. "Since the majority of breast fed infants did not develop haemorrhagic disease, the daily intake necessary for protection of those at risk must be extremely small", opined the authors. Commenting on the storage and dispensing of vitamin K, authors wrote that since 1.0 mg vitamin K was given orally and keeping in view the economy and simplicity we should use solution of 10 mg/ml (stored in amber coloured bottles) and these could be supplied in the cord care packs.

Sann et al (1985) documented that if oral vitamin K (2 mg) was given, normal or high serum vitamin K concentration could be achieved by the end of first week of life. However, it was not known whether this dose was sufficient to maintain normal serum K values and normal coagulation activities later on.

Kries et al (1985) observed that latent vitamin K deficiency without clinical evidence of bleeding could be more common than reports suggest. It was more common in Asia than in Japan. Authors documented that low oral intake and feeding of maternal milk, known to contain little vitamin K, accounted for the high FIVKA-II
K content of maternal milk was lower than that in formula,
vitamin K deficiency beyond the 4th week was observed in
only one out of 113 breast fed babies. For this, authors
provided two explanations - one was that breast fed
infants beyond the 4th week of life received more milk
because lactation was by then fully established,, secondly,
vitamin K absorption was mature.

Garrow et al (1986) measured thrombo test value
in 72 healthy full term babies. They observed that breast
fed babies from birth until 2 days after showed a
pronounced drop in thrombo test value which was prevented
by one intramuscular injection of 1.0 mg vitamin K. They
agreed with the view expressed by American Academy of
Pediatric (1961) that vitamin K should be given to all
newborn infants.

Connor et al (1986) documented that oral vitamin
K was equally effective as compared to intramuscular
vitamin K. They studied 37 infants born at home and 19
infants born in the hospital. Amongst home delivered
newborns, 18 were randomly selected to receive no vitamin
K (Group A) and 19 received 2 mg vitamin K (group B). Among
the hospital delivered babies 18 received 1 mg vitamin K
intramuscularly (group C) and remaining infants received
0.5 mg vitamin K intramuscularly. The prothrombin time of
babies in group A was significantly longer than that of
group B and C at 3rd day of life. But no difference in the
prothrombin time was found between group B and C after 3
days. Authors suggested that routine administration of an oral preparation of vitamin K at timely intervals during the first year of life would eliminate or decrease this potential fatal disorder.

Shapiro et al (1986) were of the opinion that in order to prevent late idiopathic haemorrhagic disease associated with breast feeding, all the newborn infants be given vitamin K as soon as possible after birth.

Motohara et al (1987) documented that PIVKA-II was the most sensitive test to find out the status of vitamin in the serum of infants. They documented that oral prophylaxis was more economical and simpler than intramuscular prophylaxis. They suggested that oral route was most practical when the administration was required for all newborn infants.

Tripp and McNinch (1987) documented that for reasons of acceptability to parents, safety, convenience and cost they used 1 mg oral dose of vitamin K₁ for routine prophylaxis in infants at special risk from HDN (those born prematurely or admitted to the special care baby unit or babies born to mothers taking anticonvulsants). They have suggested that in consideration of the absorption factor, which may be hampered due to some reasons, one should use more oral dose of vitamin K.

Marwaha et al (1987) documented that vitamin K deficiency must be suspected in a bleeding neonate or
disease.

Narang (1989) documented that inspite of so many controversies one should adopt the routine prophylaxis of all high risk infants. He also suggested that the recommendation should be enlarged so that all babies who would be on breast feeds should receive vitamin K prophylaxis.

Merchant et al (1989) observed that human neonate had sub-optimal stores of vitamin K at birth due to inadequate placental transfer and poor storage capacity. They have documented that early HDN (within 24 hours) caused mucosal and skin bleeds while late HDN caused bleeding in intestine and CNS. It has been suggested by the authors, that partial supplementation of diet with one or two formula feeds would be protecting against vitamin K deficiency.

Sen et al (1989) suggested that efficacy of oral vitamin in high risk infants should be evaluated. They suggested that oral vitamin K was equally effective as intramuscular vitamin K prophylaxis.

Mathur et al (1990) suggested that prophylaxis had usually been reserved for babies considered especially at risk for HDN. They have documented that there was no need to give vitamin K to full term healthy babies, but it should be given in all cases like difficult delivery and all preterm infants.