



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
Main Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2016

Prevention of vitamin K deficiency bleeding in newborn infants: a position paper by the ESPGHAN committee on nutrition

Mihatsch, Walter A; Braegger, Christian; Bronsky, Jiri; Campoy, Cristina; Domellöf, Magnus; Fewtrell, Mary; Mis, Nataša F; Hojsak, Iva; Hulst, Jessie; Indrio, Flavia; Lapillonne, Alexandre; Mlgaard, Christian; Embleton, Nicholas; van Goudoever, Johannes; ESPGHAN Committee on Nutrition

Abstract: Vitamin K deficiency bleeding (VKDB) due to physiologically low vitamin K plasma concentrations is a serious risk for newborn and young infants and can be largely prevented by adequate vitamin K supplementation. The aim of this position paper is to define the condition, describe the prevalence, discuss current prophylaxis practices and outcomes, and to provide recommendations for the prevention of VKDB in healthy term newborns and infants. All newborn infants should receive vitamin K prophylaxis and the date, dose, and mode of administration should be documented. Parental refusal of vitamin K prophylaxis after adequate information is provided should be recorded especially because of the risk of late VKDB. Healthy newborn infants should either receive 1 mg of vitamin K1 by intramuscular injection at birth; or 3 × 2 mg vitamin K1 orally at birth, at 4 to 6 days and at 4 to 6 weeks; or 2 mg vitamin K1 orally at birth, and a weekly dose of 1 mg orally for 3 months. Intramuscular application is the preferred route for efficiency and reliability of administration. The success of an oral policy depends on compliance with the protocol and this may vary between populations and healthcare settings. If the infant vomits or regurgitates the formulation within 1 hour of administration, repeating the oral dose may be appropriate. The oral route is not appropriate for preterm infants and for newborns who have cholestasis or impaired intestinal absorption or are too unwell to take oral vitamin K1, or those whose mothers have taken medications that interfere with vitamin K metabolism. Parents who receive prenatal education about the importance of vitamin K prophylaxis may be more likely to comply with local procedures.

DOI: <https://doi.org/10.1097/MPG.0000000000001232>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-134095>

Journal Article

Published Version

Originally published at:

Mihatsch, Walter A; Braegger, Christian; Bronsky, Jiri; Campoy, Cristina; Domellöf, Magnus; Fewtrell, Mary; Mis, Nataša F; Hojsak, Iva; Hulst, Jessie; Indrio, Flavia; Lapillonne, Alexandre; Mlgaard, Christian; Embleton, Nicholas; van Goudoever, Johannes; ESPGHAN Committee on Nutrition (2016). Prevention of vitamin K deficiency bleeding in newborn infants: a position paper by the ESPGHAN committee on nutrition. *Journal of Pediatric Gastroenterology and Nutrition*, 63(1):123-129.

DOI: <https://doi.org/10.1097/MPG.0000000000001232>

Prevention of Vitamin K Deficiency Bleeding in Newborn Infants: A Position Paper by the ESPGHAN Committee on Nutrition

*Walter A. Mihatsch, †Christian Braegger, ‡Jiri Bronsky, §Cristina Campoy, ||Magnus Domellöf, ¶Mary Fewtrell, #Nataša F. Mis, **Iva Hojsak, ††Jessie Hulst, †††Flavia Indrio, §§|||Alexandre Lapillonne, ¶¶##Christian Mølgaard, ***Nicholas Embleton, and †††††Johannes van Goudoever, ESPGHAN Committee on Nutrition

ABSTRACT

Vitamin K deficiency bleeding (VKDB) due to physiologically low vitamin K plasma concentrations is a serious risk for newborn and young infants and can be largely prevented by adequate vitamin K supplementation. The aim of this position paper is to define the condition, describe the prevalence, discuss current prophylaxis practices and outcomes, and to provide recommendations for the prevention of VKDB in healthy term newborns and infants. All newborn infants should receive vitamin K prophylaxis and the date, dose, and mode of administration should be documented. Parental refusal of vitamin K prophylaxis after adequate information is provided should be recorded especially because of the risk of late VKDB. Healthy newborn infants should either receive 1 mg of vitamin K₁ by intramuscular injection at birth; or 3 × 2 mg vitamin K₁ orally at birth, at 4 to 6 days and at 4 to 6 weeks; or 2 mg vitamin K₁ orally at birth, and a weekly dose of 1 mg orally

for 3 months. Intramuscular application is the preferred route for efficiency and reliability of administration. The success of an oral policy depends on compliance with the protocol and this may vary between populations and healthcare settings. If the infant vomits or regurgitates the formulation within 1 hour of administration, repeating the oral dose may be appropriate. The oral route is not appropriate for preterm infants and for newborns who have cholestasis or impaired intestinal absorption or are too unwell to take oral vitamin K₁, or those whose mothers have taken medications that interfere with vitamin K metabolism. Parents who receive prenatal education about the importance of vitamin K prophylaxis may be more likely to comply with local procedures.

Key Words: newborn infant, vitamin K, vitamin K deficiency bleeding

(*JPGN* 2016;63: 123–129)

Received March 30, 2016; accepted March 31, 2016.

From the *Department of Pediatrics, Harlaching, Munich Municipal Hospitals, Munich, Germany, the †Department of Pediatric Gastroenterology, University Children's Hospital, Zurich, Switzerland, the ‡Department Pediatrics, University Hospital Motol, Prague, Czech Republic, the §Department of Pediatrics, University of Granada, Granada, Spain, the ||Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden, the ¶Childhood Nutrition Research Centre, UCL Institute of Child Health, London, UK, the #Department of Gastroenterology, Hepatology and Nutrition, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia, the **University Children's Hospital Zagreb, Zagreb, Croatia, the ††Department of Pediatrics, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands, the †††Department of Pediatrics, University Hospital Giovanni XXIII, University Aldo Moro, Bari, Italy, the §§APHP Necker-Enfants Malades Hospital, Paris Descartes University, Paris, France, the |||CNRC, Baylor College of Medicine, Houston, TX, the ¶¶Department of Nutrition, Exercise and Sports, University of Copenhagen, København, the ##Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark, the ***Newcastle Neonatal Service, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, the ††††Department of Pediatrics, VU University Medical Center, and the ††††Department of Pediatrics, Emma Children's Hospital-AMC, Amsterdam, The Netherlands.

Address correspondence and reprint requests to Walter A. Mihatsch, MD, PhD, Department of Pediatrics Harlaching, Munich Municipal Hospital Group, Sanatoriumsplatz 2, 81545 Munich, Germany (e-mail: walter.mihatsch@klinikum-muenchen.de; familie.mihatsch@web.de).

The authors report no conflicts of interest.

Copyright © 2016 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0000000000001232

Healthy newborns and infants are at risk of developing severe hemorrhages and especially intracranial hemorrhages due to physiologically low concentrations of vitamin K that result in low concentrations of vitamin K–dependent clotting factors. Therefore prophylaxis against vitamin K deficiency bleeding (VKDB) is important.

The aim of this position paper is to define the condition, describe the prevalence, discuss current prophylaxis practices and outcomes, and to provide recommendations for setting up local guidelines for the prevention of VKDB in newborns and infants.

HISTORY OF HEMORRHAGIC DISEASE OF THE NEWBORN

Hemorrhagic disease of the newborn (1) was first systematically described by Charles Townsend in 1894 (2). He described 50 cases of a bleeding disorder that occurred in 0.6% of newborn infants usually on days 2 to 3. This is nowadays classified as the classic form of VKDB and mainly affects the skin, gastrointestinal tract, and brain. The case fatality rate was 62%, whereas surviving infants typically recovered within 5 days. At that time it was, however, impossible to differentiate sepsis-induced bleeding disorders such as disseminated intravascular coagulation from VKDB. The average incidence in unsupplemented populations has been estimated to be 0.25% to 1.7% (3) based on reported incidences of 0.25% (4), 0.33% (5) up to 13.9% (6) in a single study (also including hemorrhages of the circumcision wound).

The underlying pathophysiology was first described by the biochemist Henrik Dam. In 1929 he discovered a “Coagulation”

factor in chicken (coagulations vitamin, vitamin K) (7). Subsequently, prothrombin deficiency was documented in newborns with VKDB by Brinkhous et al (8) and Dam et al (9–15). Waddell et al (16) showed that vitamin K prevents hemorrhagic disease of the newborn. Vitamin K was first synthesized in 1939 (17) and in 1961 the committee on nutrition of the American Academy of Pediatrics first recommended postnatal prophylaxis for classic VKDB using 0.5 to 1.0 mg vitamin K parenterally or 1.0 to 2.0 mg orally (18). It is important to note that the incidence of VKDB in the USA had already significantly decreased over the years before this recommendation was published, probably because of the declining incidence of breastfeeding from 1930 to 1960. Human milk vitamin K concentration is significantly lower than infant formula vitamin K concentration and classic VKDB has mostly been seen in breastfed infants (19,20). The American Academy of Pediatrics reconfirmed its recommendation in 1993 (21). More recently, in 2003, intramuscular (IM) prophylaxis only using 0.5 to 1 mg vitamin K₁ has been recommended (3).

In 1966, the first reports from Thailand of a new VKDB syndrome were published that typically presented between 1 and 2 months of life and which is now classified as late VKDB. In 1977 Bhanchet et al (22) who first described this syndrome, summarized their studies of 93 affected predominantly breastfed (98%) Thai infants. Their incidence of intracranial bleeding was 63%. More reports from South East Asia and Australia followed. In infants without vitamin K prophylaxis the incidence of late VKDB (per 100,000 births) has been estimated to be 4.4 in the United Kingdom, 7.2 in Germany, and as high as 72 in Thailand (23). It is important to take into consideration that VKDB occurs more frequently in the Asian population compared to the Caucasian population. This may be explained by the 6-fold higher incidence of biliary atresia in Asia compared to Western Europe (24).

In infants born to mothers using anticonvulsant drugs (eg, phenobarbital, phenytoin, carbamazepine, etc) an increased incidence of early VKDB within the first 24 hours has been observed (25,26). More recent data critically discussed this association; however, a causal link cannot be excluded (27). Postnatal IM vitamin K corrects biochemical abnormalities in these infants within 2 hours (27). Prenatal maternal vitamin K treatment has been hypothesized to prevent early VKDB in these infants (28); however, this concept still warrants further evaluation (29). Therefore, immediate postnatal IM Vitamin K administration is currently regarded as the optimum VKDB prophylaxis for this group of infants.

VITAMIN K

Vitamin K is a family of fat-soluble 2-methyl-1,4-naphthoquinones with a variable alkyl substituent at the 3 position (19,30). Vitamin K is required for the γ -carboxylation of coagulation factors II (prothrombin), VII, IX, X, protein C, and protein S. It acts as an essential cofactor for the conversion of specific peptide-bound glutamate residues to γ -carboxylglutamate residues. The collective abbreviation for these under-carboxylated molecules is PIVKA (proteins induced by vitamin K absence), and includes, for example, PIVKA-II, which is the glutamate precursor of prothrombin (factor II). There are additional vitamin-K-dependent proteins such as osteocalcin or matrix GLA protein the function of which is less clear.

Relevant Forms of Vitamin K

- (1) Phylloquinone (vitamin K₁) is synthesized by plants and algae, for example, green leafy vegetables such as spinach, brussels sprouts, cabbage, lettuce, and broccoli. This is the only form used therapeutically in humans.

- (2) Multiple menaquinones (vitamin K₂), synthesized by bacteria such as intestinal bacteria and found in egg yolk, chicken, beef, liver, fermented products such as cheese, and in fermented vegetables such as cabbage or natto (fermented soybeans).
- (3) The synthetic form menadiolone (vitamin K₃) is no longer used for oral vitamin K prophylaxis because of potential toxicity. Hemolytic anemia has been reported in glucose-6-phosphate dehydrogenase deficient infants treated with vitamin K₃.

The intestinal absorption of dietary vitamin K, mainly phylloquinone (vitamin K₁), is thought to be governed by the same principles established for other fat-soluble vitamins, and in healthy adults the efficiency of absorption is about 80% (19). Phylloquinone is the major circulating form of vitamin K but in addition there are small amounts of menaquinones (vitamin K₂) (19). Although phylloquinone in blood must have been derived exclusively from the diet, it is not known whether circulating menaquinones are derived from the diet, intestinal flora, or both. Human liver stores normally comprise about 90% menaquinones and 10% phylloquinone (31). Functionally, menaquinones seem to be less important because dietary phylloquinone deficiency induces subclinical signs of vitamin K deficiency without a change of hepatic menaquinone stores (32). Hepatic menaquinone stores may not be available to microsomal γ -glutamyl carboxylase (31). There is no menaquinone detectable in newborns (33–35), and at 1 year of age hepatic menaquinone stores are still significantly lower than that in adults (32,34).

Vitamin K does not easily cross the placenta and the average maternal/fetal concentration gradient is within the range of 20:1 to 40:1 (19). The fetal plasma vitamin K concentration is very low and consequently at birth concentrations of clotting factors are low. Increased PIVKA II concentrations (>10 ng/mL) have been found in the umbilical cord blood in 10% to 50% of healthy term and preterm infants, which is a biomarker of low vitamin K level (36,37). At least a transient increase in fetal vitamin K₁ concentration has been observed with maternal vitamin K₁ supplementation; however, no significant effect on vitamin K-dependent coagulation factors has been found (19). Therefore prenatal maternal vitamin K₁ supplementation does not prevent VKDB.

CLASSIFICATION OF VITAMIN K DEFICIENCY BLEEDING IN NEWBORN INFANTS AND INFANTS

VKDB of the newborn has been classified (19,38) by age of onset into early (<24 hours), classical (days 1–7) and late (>1 week <6 months), and by etiology into idiopathic and secondary in 1999 by the Pediatric and Perinatal Subcommittee of the International Society on Thrombosis and Hemostasis (39). There are few data on the relative frequencies of early, classic, and late VKDB. A regional epidemiological study from Malaysia in the 1990s, however, enables calculation of a lower threshold of the incidences (40). Within a 2-year period 42 VKDB infants were admitted to a single regional pediatric hospital likely to provide care for all such infants. In a population in which most infants were breastfed (96%) and in which vitamin K prophylaxis was infrequent (83% not supplemented) the incidences of early, classic and late VKDB were at least 1/7000, 1/4000, and 1/8000, respectively. The relative proportions were 6:10:5 (Table 1).

VITAMIN K METABOLISM OF THE NEWBORN AND RISK FACTORS FOR VKDB

Although plasma vitamin K₁ concentration is very low immediately after birth, adult levels have been recorded on days

TABLE 1. Classification of vitamin K deficiency bleeding of the newborn infant (41)

Syndrome	Time of presentation	Common bleeding sites (28,38,42)	Comments
Early VKDB	0–24 h	Subperiosteal hemorrhage of the skull (cephalohematoma), intracranial, brain, intrathoracic, intra-abdominal, umbilical stump	Maternal drugs are a frequent cause (eg, coumarin-anticoagulants such as warfarin, enzyme-inducing drugs, eg, anticonvulsants, and some tuberculostatic drugs) (28,43–46)
Classic VKDB	2–7 days (2)	Gastrointestinal tract, skin, adrenal gland, nose, wound from circumcision, intracranial, umbilical stump	Mainly idiopathic, maternal drugs (18,42,47,48)
Late VKDB	2–12 wk (23,49–52)	Intracranial, skin, gastrointestinal	Most commonly presenting feature of underlying disease resulting in reduced vitamin K absorption (eg, cystic fibrosis, biliary atresia, or other liver diseases with cholestasis), occasionally idiopathic

VKDB = vitamin K deficiency bleeding.

3 to 4 following supplementation (53,54) and levels are higher in formula-fed infants compared to breastfed infants. Human milk vitamin K₁ concentration (median 2.5 µg/L [0.85–9.2 µg/L]) is significantly lower than currently available formula milk (4–25 µg/100 kcal approximately corresponding to 24–175 µg/L) (55,56). On average daily vitamin K₁ intake of breastfed infants is <1 µg within the first 6 months of life, whereas the intake of formula-fed infants is on average up to 100 times higher (57). With regard to global coagulation tests such as prothrombin time (PT) there is no significant difference between breast- and formula-fed infants (53,57). PIVKAs are, however, much more commonly reported in breastfed infants (54,58). Formula vitamin K₁ exceeds the recommended vitamin K intake of at least 5 µg/day (30). Because breastfeeding fails to provide this intake, and because VKDB is much more common in unsupplemented breastfed infants it is recommended that all infants receive some form of supplementation.

The major risk factor for classic VKDB is a low plasma vitamin K concentration, due to low levels in breast milk and/or inadequate vitamin K prophylaxis in newborn infants, all of whom are vitamin K deficient at birth. The effects are manifest by the presence of PIVKA and lower levels of vitamin K-dependent coagulation factors and of other vitamin K-dependent proteins such as the osteoblast product, osteocalcin. Elevated PIVKA-II levels (>10 ng/mL) have been found in the umbilical cord blood of 10% to 50% of healthy preterm or term newborn infants (36,37). At the age of 4 to 5 days PIVKA have been found in up to 70% of healthy unsupplemented newborn infants (59). In addition, factor II and VII activity has been reported to be reduced in infants who did not achieve a breastfeeding volume of 100 mL/kg at 3 to 4 days of age (59). Therefore classic VKDB may at least partially be a consequence of insufficient or delayed establishment of breastfeeding (59). Intramuscular or oral (1.0 mg) vitamin K prophylaxis has been found to be equally effective in improving biochemical indices of coagulation status (PIVKA) at 1 to 7 days (60–62).

The major risk factors for late VKDB are low plasma vitamin K concentrations due to insufficient vitamin K prophylaxis, and breastfeeding combined with cholestatic liver impairment, which may be subclinical or transient (63,64).

SAFETY OF VITAMIN K PREPARATIONS

There are no data to determine the upper safe level of vitamin K in general in infancy. In 1992 Jean Golding et al (65) published epidemiological data suggesting that certain forms of childhood cancer were associated with IM vitamin K injections. The

speculated biological mechanism of carcinogenesis (induction of sister chromatid exchange) did not accord with other information from the literature about *in vivo* effects of vitamin K or other tests of carcinogenicity (21). Most expert opinion currently suggest that a causal relation between IM injection of vitamin K and childhood cancer is not plausible (3,23) and the hypothesized association has never been confirmed in other large epidemiological studies. On the contrary, due to the lack of large randomized studies, this hypothesis has not been disproved (66,67).

DIAGNOSIS OF VITAMIN K DEFICIENCY BLEEDING

A confirmed case of VKDB should fulfill the criteria of having a PT that is ≥ 4 times the control value and display at least one of the following (68):

- (1) Normal or raised platelet count, normal fibrinogen, and absent fibrin degradation products.
- (2) PT returning to normal within 30 to 20 minutes after intravenous vitamin K administration (69,70). In general there is no need for supplementation of coagulation factors (41).
- (3) PIVKA (usually that of factor II) level exceeding normal controls (41).

PROPHYLAXIS FOR VITAMIN K DEFICIENCY BLEEDING

Intramuscular Injection of Vitamin K

In 1961 and 1993 the American Academy of Pediatrics recommended early postnatal vitamin K prophylaxis using 0.5 to 1.0 mg vitamin K parenteral or 1.0 to 2.0 mg orally (18,21). In 2003 the IM injection of 1 mg vitamin K at birth was proposed as standard of care of healthy newborn infants (3). The argument in favor of IM prophylaxis was that a single injection was more reliably administered, and likely to result in a depot supply over the ensuing weeks of risk. Therefore this policy is widely used worldwide. Epidemiological surveillance data have shown that this policy virtually prevents classic and late VKDB (incidence <0.2/100,000) (23,68,71,72). Despite the use of postnatal 1 mg IM injection there are still some rare cases of late VKDB, which warrant further evaluation (41,73–75). Adverse effects of IM vitamin K injections such as local infections have never been systematically assessed; however, it is likely to be painful for newborn infants.

Oral Supplementation of Vitamin K

Worldwide, oral supplementation became more widespread after the article by Golding et al in 1992 (65) and is still used despite the association between IM vitamin K and childhood cancer never being reconfirmed (66,67).

Oral vitamin K prophylaxis policies vary in terms of dose and frequency, and appear to offer virtually complete protection from early and classic bleeding. The associated incidence of late VKDB has, however, repeatedly been observed to be higher when compared to a single 1 mg IM dose at birth (23,68,76,77).

In order to prevent late VKDB in addition to early and classic bleeding in Europe 3 oral prophylaxis patterns have been developed and evaluated. Because there are no randomized head-to-head comparison trials, and such trials will probably never be conducted, efficiency of individual policies can only be assessed by surveillance data. These data are always at risk of underreporting (78).

In Germany using a 3 × 2 mg oral vitamin K₁ prophylaxis policy an incidence of late VKDB of 0.44/100,000 (95% CI 0.19–0.87) has been reported (79). Taking an underreporting bias of 57% (38%–76%) (78) into account the estimated incidence was 0.73/100,000 (95% CI 0.23–2.2). In Switzerland in 458,184 newborn infants in 2005 to 2011 one early (18 hours of age) and 4 late VKDB cases were observed (80). All infants were breastfed and in all but one of the infants the parents declined vitamin K prophylaxis. In the remaining infant only the first 2 oral vitamin K doses had been given. All infants with late VKDB had some cholestatic liver disease. Therefore, in infants with complete VKDB prophylaxis (oral 3 × 2 mg) there was a combined risk for classic and late VKDB of 0/100,000 (95% CI 0–0.81) (80). The degree of underreporting in the Swiss study is, however, unknown. At 24 weeks of age an additional fully breastfed infant developed very late VKDB, in the absence of cholestatic liver disease. Of note these published efficacy data depended on administration of oral vitamin K by health-care professionals (Table 2).

Taking these data together, there is some evidence that the oral 3 × 2 mg policy may be less effective than a single postnatal 1 mg IM injection (73,79). In all infants with late VKDB, there was a combination of previously unknown cholestatic liver disease together with breastfeeding. In infants with conjugated hyperbilirubinemia intestinal absorption of oral vitamin K prophylaxis is unreliable (90).

In contrast to promising early data (68,91) on the previous Dutch oral policy (1 mg after birth followed by 25 µg/day for weeks 2–13) later extensive surveillance data suggested that this policy was associated with the highest incidence of late VKDB of all the policies listed in the table above (85). Concerning the cause of the 6 reported cases of late VKDB there was 1 case of idiopathic VKDB, 1 case in association with breast milk jaundice, and 4 cases of previously unrecognized cholestasis because of biliary atresia. In the Netherlands annually approximately 5 infants experienced serious hemorrhage. After evaluation of current literature and advice from The Health Council of the Netherlands, vitamin K dosage was adapted for all breastfed infants from day 8 to 3 months (12th week of life) following birth by raising the daily dose from 25 to 150 µg/day (84). This policy, however, still warrants epidemiological evaluation.

In Denmark, no cases of VKDB were reported during a period when the following policy was used: 2 mg oral at birth and 1 mg weekly orally administered vitamin K during the first 3 months of life. This was given to at least 400,000 infants during a 9-year surveillance period (88,89). Importantly, in infants with previously unknown biliary atresia this regimen seemed to be as effective as the single postnatal 1 mg IM injection (92). Weekly oral administration of 1 mg requires a higher degree of parental compliance than an oral policy of 3 × 2 mg vitamin K₁ postnatal, on day 3 to 10, and at 4 to 6 weeks. In 2000 in Denmark the National Board of Health (Sundhedsstyrelsen) evaluated the literature and concluded that IM prophylaxis gave better protection against VKDB, alongside a recognition that IM injection had no apparent relation with

TABLE 2. Recent surveillance data of vitamin K deficiency bleeding prophylaxis policies (efficacy is given ATP)

VKDB prophylaxis policy	Country	Evaluated in N infants	Associated classic/late VKDB incidence per 100,000
Oral prophylaxis 3 × 2 mg			
3 × 2 mg oral (postnatally, days 3–10 and weeks 4–6)	Germany	1,817,769	0.44 (95% CI 0.19–0.87) (79); taking underreporting (78) into account the estimated incidence may be 0.73 (95% CI 0.23–2.2) 76
	Switzerland	458,184	0.0 (95% CI 0.0–0.81) (80)
Total		2,275,953	8 Cases 0.35 (95% CI 0.16–0.69) (79,80)
1 mg IM prophylaxis			
1 mg IM postnatally	New Zealand	654,000	0.16 (95% CI 0–0.46) (72)
No uniform policy (73,81–83) most commonly 1 mg IM postnatally but several regions use oral	UK	1,700,000	0.24 (0.0–0.35) (73)
Total		2,354,000	5 cases 0.21 (95% CI 0.06–0.5) (72,73)
Policies no longer in reported use			
1 mg oral postnatally; 25 µg/day oral days 8–90	The Netherlands (until 2011) (84)	187,910	3.2 (95% CI 1.2–6.9) (85)
2 mg oral postnatally; 1 mg/wk oral for 3 mo	Denmark (until 2000) (86,87)	400,000	0.0 (95% CI 0.0–0.9) (88,89)

CI = confidence interval; VKDB = vitamin K deficiency bleeding.

the risk of cancer. Therefore, postnatal 1 mg IM vitamin K prophylaxis was recommended as the standard of care (86). In addition at this time it was no longer possible to obtain the oral preparation of vitamin K because of technical problems (73). This recommendation was reconfirmed in 2010 (87).

In Great Britain in 2006 routine vitamin K prophylaxis was recommended by the National Institute for Clinical Excellence (NICE) to be administered as a single dose of 1 mg IM as this is the most efficacious and cost-effective method of administration (83). Alternatively (second line), 2 doses of 2 mg oral vitamin K should be given at birth and at 4 to 7 days and a third dose in exclusively breastfed infants only at 1 month. As a third alternative, the Danish regimen may be used (81,82).

Finally it is important to consider that although there are no randomized head-to-head comparison trials comparing different policies, these are unlikely given the low incidence of VKDB in supplemented infants.

VITAMIN K PREPARATIONS

The available data do not permit the recommendation of one specific vitamin K preparation. Pharmacokinetic studies of a mixed micellar vitamin K preparation suggested a higher oral bioavailability compared with a normal vitamin K preparation (93). This theoretical advantage of the pediatric mixed micellar preparation of vitamin K has never been demonstrated in randomized controlled trials (76). Of note, the data suggesting better oral bioavailability were based on only 3 children experiencing cholestasis (93). In Germany surveillance of late VKDB observed no significant benefit of the mixed micellar vitamin K preparation (RR 0.58; 95% CI 0.23–1.47). Because of the low incidence of late VKDB (18 infants) the sample size of 3.2 million children was, however, insufficient to detect a significant difference (79).

In contrast to IM injections, an oral vitamin K policy may be easier to achieve, and may also be more acceptable to some parents and healthcare providers. Unpredictable absorption, unclear compliance with repeated dosing, insufficient parental health access (eg, minorities, asylum seeker, and refugees), and incomplete application (eg, possetting or vomiting that requires repeat administration) remain important disadvantages. A variety of different products are used; however, caution must be taken, because a number of these may not have undergone pharmaceutical quality control.

The pharmacokinetics of intravenous (IV) vitamin K are not very well known, but it is likely similar to that of vitamin K given orally. IV administration does not seem to bring the same efficiency as the IM route for the prevention of the late form of VKDB especially if the injection is not repeated (73). The slower increase in urinary excretion of vitamin K metabolites after IM injection compared with an equivalent dose given by the IV route gives support to a depot effect whereby lipophilic vitamin K₁ leaches out slowly from the muscular site of injection into the circulation. In contrast the rapid increase in urinary excretion of vitamin K metabolites after IV injection suggest a more rapid but transient effect of the IV injection (94). IV vitamin K₁ administration may be considered in preterm infants, sick term infants, or infants with cholestatic liver disease. The use of IV vitamin K₁ has, however, not been extensively examined for prophylaxis of VKDB.

CONCLUSIONS

- (1) VKDB due to physiologically low vitamin K plasma concentrations is a serious risk for newborn and young infants.
- (2) Adequate vitamin K supplementation prevents the vast majority of VKDB.

- (3) Intramuscular application is the preferred route for efficiency and reliability of administration.

Data from some countries suggest IM application may be more effective than 3 × 2 mg oral prophylaxis for prevention of late VKDB (68,71,79,95). Analysis of the more recent epidemiological data obtained from >4.5 million children (Table 2) does not suggest a significant difference between these 2 options with regard to the efficacy in prevention of late VKDB.

RECOMMENDATIONS

- (1) All newborn infants should receive vitamin K prophylaxis.
- (2) Vitamin K prophylaxis and the mode of administration should be documented.
- (3) Parental refusal of vitamin K prophylaxis after adequate information is provided should be documented especially because of the risk of late VKDB (96,97).
- (4) Healthy newborn infants should either receive:
 - (a) 1 mg of Vitamin K₁ by IM injection at birth, or
 - (b) 3 × 2 mg Vitamin K₁ orally at birth, at 4 to 6 days and at 4 to 6 weeks. or
 - (c) 2 mg Vitamin K₁ orally at birth, and a weekly dose of 1 mg orally for 3 months.
- (5) The success of an oral policy depends on compliance with the protocol and this may vary between populations and healthcare settings. If the infant vomits or regurgitates the formulation within 1 hour of administration, repeating the oral dose may be appropriate.
- (6) The oral route is not appropriate for preterm infants and for newborns who are unwell, have cholestasis or impaired intestinal absorption or are unable to take oral vitamin K, or those whose mothers have taken medications that interfere with vitamin K metabolism.

General Advice

- (1) Healthcare providers must develop local policies, procedures, and guidelines for the administration of prophylactic vitamin K to infants, and conduct regular audit to ensure compliance and efficacy. The date, dose, and route of administration must be recorded in the infant's personal health record (expert opinion of the committee).
- (2) Parents who receive information during the antenatal period about the importance of vitamin K prophylaxis may be more likely to comply with local procedures (98).

FUTURE RESEARCH TOPICS

- (1) Robust national surveillance data of VKDB, which require accurate documentation of policies and procedures.
- (2) Efficacy and quality control of individual vitamin K products used for supplementation.

REFERENCES

1. McNinch A. Vitamin K deficiency bleeding: early history and recent trends in the United Kingdom. *Early Hum Dev* 2010;86(suppl 1):63–5.

2. Townsend CW. The haemorrhagic disease of the newborn. *Arch Paediatr* 1994;11:652–3.
3. American Academy of Pediatrics. Controversies concerning vitamin K and the newborn. American Academy of Pediatrics Committee on Fetus and Newborn. *Pediatrics* 2003;112:191–2.
4. Smith CH. Blood Diseases of Infancy and Childhood. St. Louis: Mosby; 1960.
5. Aballi AJ, Lopez Banus V, De Lamerens S, et al. Coagulation studies in the newborn period; alterations of thromboplastin generation and effects of vitamin K in full-term and premature infants. *AMA J Dis Child* 1957;94:589–600.
6. Vietti TJ, Murphy TP, James JA, et al. Observations on the prophylactic use of vitamin K in the newborn infant. *J Pediatr* 1960;56:343–6.
7. Dam H, Schönheyder F, Tage-Hansen H. Cholesterolfstoffwechsel in Hühnereiern und Hühnchen. *Biochem Z* 1929;215:475–92.
8. Brinkhous KM, Smith BK, Warner BW. Plasmaprotein level in normal infancy and hemorrhagic disease of the newborn. *Am J Med Sci* 1937;193:475–80.
9. Dam H, Schönheyder F, Tage-Hansen E. Studies on the mode of action of vitamin K. *Biochem J* 1936;30:1075–9.
10. Dam H, Dyggve H, Larsen H, et al. The relation of vitamin K deficiency to hemorrhagic disease of the newborn. *Adv Pediatr* 1952;5:129–53.
11. Dam H, Tage-Hansen E. Vitamin-K lack in normal and sick infants. *Lancet* 1939;2:1157–62.
12. Hellmann LM, Shettles LB. Factors influencing plasma prothrombin in the newborn infant I. Prematurity and vitamin K. *Bull Hopkins Hosp* 1939;65:138–41.
13. Owen A. Blood coagulation during infancy. *Proc Soc Exp Biol Med* 1939;41:181–8.
14. Shettles LB, Delfs E, Hellmann LM. Factors influencing plasma prothrombin in newborn infants. II. Antepartum and neonatal ingestion of vitamin K concentrate. *Bull Hopkins Hosp* 1939;65:419–26.
15. Quick AJ, Grossmann AM. The nature of the hemorrhagic disease of the newborn: delayed restoration of the prothrombin level. *Am J Med Sci* 1940;199:1–9.
16. Waddell WW, Guerry D, Bray WE, et al. Possible effects of vitamin K on prothrombin and clotting time in newly-born infants. *J Path Bact* 1937;44:633–5.
17. Almquist HJ, Close AA. Synthetic and natural antihemorrhagic compounds. *Am J Chem Soc* 1939;61:2557–8.
18. American Academy of Pediatrics. Report of the Committee on Nutrition: vitamin K compounds and the water-soluble analogues. *Pediatrics* 1961;28:501–6.
19. Shearer MJ. Vitamin K metabolism and nutrition. *Blood Rev* 1992;6:92–104.
20. McNinch AW, Orme RL, Tripp JH. Haemorrhagic disease of the newborn returns. *Lancet* 1983;1:1089–90.
21. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993;91:1001–3.
22. Bhanchet P, Tuchinda S, Hathirat P, et al. A bleeding syndrome in infants due to acquired prothrombin complex deficiency: a survey of 93 affected infants. *Clin Pediatr (Phila)* 1977;16:992–8.
23. Von Kries R, Hanawa Y. Neonatal vitamin K prophylaxis. Report of Scientific and Standardization Subcommittee on Perinatal Haemostasis. *Thromb Haemost* 1993;69:293–5.
24. Chardot C. Biliary atresia. *Orphanet J Rare Dis* 2006;1:28.
25. Evans AR, Forrester RM, Discombe C. Neonatal haemorrhage following maternal anticonvulsant therapy. *Lancet* 1970;1:517–8.
26. Laosombat V. Hemorrhagic disease of the newborn after maternal anticonvulsant therapy: a case report and literature review. *J Med Assoc Thai* 1988;71:643–8.
27. Hey E. Effect of maternal anticonvulsant treatment on neonatal blood coagulation. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F208–10.
28. Deblay MF, Vert P, Andre M, et al. Transplacental vitamin K prevents haemorrhagic disease of infant of epileptic mother. *Lancet* 1982;1:1247.
29. Rezvani M, Koren G. Does vitamin K prophylaxis prevent bleeding in neonates exposed to enzyme-inducing antiepileptic drugs in utero? *Can Fam Physician* 2006;52:721–2.
30. F.A.O., WHO. Vitamin K. In: Nantel G, Tontisirin K, eds. *Human Mineral and Vitamin Requirements*. Rome: Food and Nutrition Division FAO; 2001:133–50.
31. Suttie JW. The importance of menaquinones in human nutrition. *Annu Rev Nutr* 1995;15:399–417.
32. Usui Y, Tanimura H, Nishimura N, et al. Vitamin K concentrations in the plasma and liver of surgical patients. *Am J Clin Nutr* 1990;51:846–52.
33. Shearer MJ, McCarthy PT, Crampton OE, et al. The assessment of human vitamin K status from tissue measurements. In: Suttie JW, ed. *Current Advances in Vitamin K Research*. New York: Elsevier; 1988: 437–52.
34. Kayata S, Kindberg C, Greer FR, et al. Vitamin K1 and K2 in infant human liver. *J Pediatr Gastroenterol Nutr* 1989;8:304–7.
35. Shirahata A, Nakamura T, Ariyoshi N. Vitamin K1 and K2 in contents in blood, stool, and liver tissues of neonates and young infants. In: Suzuki S, Hathaway WE, Bonnar J, Sutor AH, eds. *Perinatal Thrombosis and Hemostasis*. Tokyo: Springer-Verlag; 1991:213–23.
36. Kumar D, Greer FR, Super DM, et al. Vitamin K status of premature infants: implications for current recommendations. *Pediatrics* 2001;108:1117–22.
37. Greer FR, Marshall SP, Severson RR, et al. A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. *Arch Dis Child* 1998;79:300–5.
38. Lane PA, Hathaway WE. Vitamin K in infancy. *J Pediatr* 1985;106:351–9.
39. Sutor AH, von Kries R, Cornelissen EA, et al. Vitamin K deficiency bleeding (VKDB) in infancy. ISTH Pediatric/Perinatal Subcommittee. International Society on Thrombosis and Haemostasis. *Thromb Haemost* 1999;81:456–61.
40. Choo KE, Tan KK, Chuah SP, et al. Haemorrhagic disease in newborn and older infants: a study in hospitalized children in Kelantan, Malaysia. *Ann Trop Paediatr* 1994;14:231–7.
41. Shearer MJ. Vitamin K deficiency bleeding (VKDB) in early infancy. *Blood Rev* 2009;23:49–59.
42. McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. *BMJ* 1991;303:1105–9.
43. Cornelissen M, Steegers-Theunissen R, Kollee L, et al. Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. *Am J Obstet Gynecol* 1993;168:884–8.
44. Cornelissen M, Steegers-Theunissen R, Kollee L, et al. Increased incidence of neonatal vitamin K deficiency resulting from maternal anticonvulsant therapy. *Am J Obstet Gynecol* 1993;168:923–8.
45. Mountain KR, Hirsh J, Gallus AS. Neonatal coagulation defect due to anticonvulsant drug treatment in pregnancy. *Lancet* 1970;1:265–8.
46. Thorp JA, Parriott J, Ferrette-Smith D, et al. Antepartum vitamin K and phenobarbital for preventing intraventricular hemorrhage in the premature newborn: a randomized, double-blind, placebo-controlled trial. *Obstet Gynecol* 1994;83:70–6.
47. Von Kries R. Vitamin K prophylaxis—a useful public health measure? *Paediatr Perinat Epidemiol* 1992;6:7–13.
48. Sutherland JM, Glueck HI, Gleser G. Hemorrhagic disease of the newborn. Breast feeding as a necessary factor in the pathogenesis. *Am J Dis Child* 1967;113:524–33.
49. Loughnan P, McDougall PM. The duration of vitamin K₁ efficacy: is intramuscular vitamin K₁ acting as a depot preparation? In: Sutor AH, Hathaway WE, eds. *Vitamin K in Infancy*. Stuttgart, New York: Schattauer; 1995.
50. Sutor AH, Dagnes N, Niederhoff H. Late form of vitamin K deficiency bleeding in Germany. *Klin Padiatr* 1995;207:89–97.
51. Hanawa Y, Maki M, Matsuyama E, et al. The third nationwide survey in Japan of vitamin K deficiency in infancy. *Acta Paediatr Jpn* 1990;32:51–9.
52. Chau WT, Chou ML, Eitzman DV. Intracranial hemorrhage and vitamin K deficiency in early infancy. *J Pediatr* 1984;105:880–4.
53. Pietersma-de Bruyn AL, Van Haard PM, Beunis MH, et al. Vitamin K1 levels and coagulation factors in healthy term newborns till 4 weeks after birth. *Haemostasis* 1990;20:8–14.
54. Widdershoven J, Lambert W, Motohara K, et al. Plasma concentrations of vitamin K1 and PIVKA-II in bottle-fed and breast-fed infants with and without vitamin K prophylaxis at birth. *Eur J Pediatr* 1988;148:139–42.
55. Haroon Y, Shearer MJ, Rahim S, et al. The content of phylloquinone (vitamin K1) in human milk, cows' milk and infant formula foods determined by high-performance liquid chromatography. *J Nutr* 1982;112:1105–17.

56. Russell R, Beard JL, Cousins R, et al. Vitamin K. In: IOM, ed. Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press; 2001:162–96.
57. Greer FR. Vitamin K status of lactating mothers and their infants. *Acta Paediatr Suppl* 1999;88:95–103.
58. Von Kries R, Kreppel S, Becker A, et al. Acarboxyprothrombin concentration [corrected] after oral prophylactic vitamin K. *Arch Dis Child* 1987;62:938–40.
59. Von Kries R, Becker A, Göbel U. Vitamin K in the newborn: influence of nutritional factors on a carboxy-prothrombin detectability and factor II and VII clotting activity. *Eur J Pediatr* 1987;146:123–7.
60. Motohara K, Endo F, Matsuda I. Effect of vitamin K administration on acarboxy prothrombin (PIVKA-II) levels in newborns. *Lancet* 1985;2:242–4.
61. Sharma RK, Marwaha N, Kumar P, et al. Effect of oral water soluble vitamin K on PIVKA-II levels in newborns. *Indian Pediatr* 1995;32:863–7.
62. Ulusahin N, Arsan S, Ertogan F. Effects of oral and intramuscular vitamin K prophylaxis on PIVKA-II assay parameters in breastfed infants in Turkey. *Turk J Pediatr* 1996;38:295–300.
63. Von Kries R, Reifenhauer A, Göbel U, et al. Late onset haemorrhagic disease of newborn with temporary malabsorption of vitamin K1. *Lancet* 1985;1:1035.
64. Matsuda I, Nishiyama S, Motohara K, et al. Late neonatal vitamin K deficiency associated with subclinical liver dysfunction in human milk-fed infants. *J Pediatr* 1989;114:602–5.
65. Golding J, Greenwood R, Birmingham K, et al. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992;305:341–6.
66. Fear NT, Roman E, Ansell P, et al. Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003;89:1228–31.
67. Roman E, Fear NT, Ansell P, et al. Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. *Br J Cancer* 2002;86:63–9.
68. Cornelissen M, Von Kries R, Loughnan P, et al. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. *Eur J Pediatr* 1997;156:126–30.
69. Flood VH, Galderisi FC, Lowas SR, et al. Hemorrhagic disease of the newborn despite vitamin K prophylaxis at birth. *Pediatric Blood Cancer* 2008;50:1075–7.
70. Sutor AH, Kuenzer W. Time interval between vitamin K administration and effective hemostasis. In: Suzuki S, Hathaway WE, Bonnar J, Sutor AH, eds. *Perinatal Thrombosis and Hemostasis*. Tokyo: Springer Verlag; 1991.
71. McNinch A, Busfield A, Tripp J. Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993–94 and 2001–02. *Arch Dis Child* 2007;92:759–66.
72. Darlow BA, Phillips AA, Dickson NP. New Zealand surveillance of neonatal vitamin K deficiency bleeding (VKDB): 1998–2008. *J Paediatr Child Health* 2011;47:460–4.
73. Busfield A, Samuel R, McNinch A, et al. Vitamin K deficiency bleeding after NICE guidance and withdrawal of Konakion Neonatal: British Paediatric Surveillance Unit study. *Arch Dis Child* 2013;98:41–7.
74. Ciantelli M, Bartalena L, Bernardini M, et al. Late vitamin K deficiency bleeding after intramuscular prophylaxis at birth: a case report. *J Perinatol* 2009;29:168–9.
75. Chuansumrit A, Isarangkura P, Hathirat P. Vitamin K deficiency bleeding in Thailand: a 32-year history. *Southeast Asian J Trop Med Public Health* 1998;29:649–54.
76. Von Kries R, Hachmeister A, Göbel U. Can 3 oral 2 mg doses of vitamin K effectively prevent late vitamin K deficiency bleeding? *Eur J Pediatr* 1999;158(suppl 3):S183–6.
77. Schubiger G, Berger TM, Weber R, et al., Swiss Paediatric Surveillance U. Prevention of vitamin K deficiency bleeding with oral mixed micellar phylloquinone: results of a 6-year surveillance in Switzerland. *Eur J Pediatr* 2003;162:885–8.
78. Von Kries R, Heinrich B, Hermann M. [German paediatric surveillance unit (ESPED)]. *Monatsschr Kinderheilkd* 2002;149:1191–7.
79. Von Kries R, Hachmeister A, Göbel U. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F109–12.
80. Laubscher B, Bänziger O, Schubiger G, et al. Prevention of vitamin K deficiency bleeding with three oral mixed micellar phylloquinone doses: results of a 6-year (2005–2011) surveillance in Switzerland. *Eur J Pediatr* 2013;172:357–60.
81. Pediatric Formulary Committee. Vitamin K. In: Pediatric Formulary Committee, ed. *BNF for Children*. London: Pharmaceutical Press and PCPCH Publications; 2013:Chapter 9.96: 486–7.
82. Pediatric Formulary Committee. BNF for Children (online). London: BMJ Group, Pharmaceutical Press, and PCPCH Publications; 2014.
83. McCandlish R, Adams C, Barry C, et al. Routine postnatal care of women and their babies. NICE clinical guideline 37. 2006. <http://www.nice.org.uk/guidance/cg37/evidence/cg37-postnatal-care-full-guideline3>. Accessed February 7, 2015.
84. De Winter JP, Joosten KF, Ijland MM, et al. New Dutch practice guideline for administration of vitamin K to full-term newborns. *Ned Tijdschr Geneesk* 2011;155:A936.
85. Ijland MM, Pereira RR, Cornelissen EA. Incidence of late vitamin K deficiency bleeding in newborns in the Netherlands in 2005: evaluation of the current guideline. *Eur J Pediatr* 2008;167:165–9.
86. Krag E, Skak-Iversen L. Communication of May the 23rd 2000 on the amended guidelines on the use of Vitamin K in newborn infants and infants for birthplaces, midwives, health visitors and general practitioners. Danish National Board of Health, 2010. http://sundhedsstyrelsen.dk/publ/Off_Medd/official_meddelelse_k_vitamin1.pdf. Accessed February 7, 2015.
87. Gotrik JK, Smith E. Health guidance on healthcare related vitamin and iron supplements in newborn infants and infants. Danish National Board of Health, 2010. http://sundhedsstyrelsen.dk/publ/publ2010/cff/jern/vejledning_jern-_og_vitaminer.pdf. Accessed February 7, 2015.
88. Hansen KN, Minousis M, Ebbesen F. Weekly oral vitamin K prophylaxis in Denmark. *Acta Paediatr* 2003;92:802–5.
89. Hansen KN, Ebbesen F. Neonatal vitamin K prophylaxis in Denmark: three years' experience with oral administration during the first three months of life compared with one oral administration at birth. *Acta Paediatr* 1996;85:1137–9.
90. Pereira SP, Shearer MJ, Williams R, et al. Intestinal absorption of mixed micellar phylloquinone (vitamin K1) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F113–8.
91. Cornelissen EA, Kollee LA, van Lith TG, et al. Evaluation of a daily dose of 25 micrograms vitamin K1 to prevent vitamin K deficiency in breast-fed infants. *J Pediatr Gastroenterol Nutr* 1993;16:301–5.
92. Van Hasselt PM, De Koning TJ, Kvist N, et al. Prevention of vitamin K deficiency bleeding in breastfed infants: lessons from the Dutch and Danish biliary atresia registries. *Pediatrics* 2008;121:e857–63.
93. Amedee-Manesme O, Lambert WE, Alagille D, et al. Pharmacokinetics and safety of a new solution of vitamin K1(20) in children with cholestasis. *J Pediatr Gastroenterol Nutr* 1992;14:160–5.
94. Harrington DJ, Clarke P, Card DJ, et al. Urinary excretion of vitamin K metabolites in term and preterm infants: relationship to vitamin K status and prophylaxis. *Pediatr Res* 2010;68:508–12.
95. Busfield A, McNinch A, Tripp J. Neonatal vitamin K prophylaxis in Great Britain and Ireland: the impact of perceived risk and product licensing on effectiveness. *Arch Dis Child* 2007;92:754–8.
96. Centers for Disease Control and Prevention. Notes from the field: late vitamin K deficiency bleeding in infants whose parents declined vitamin K prophylaxis—Tennessee, 2003. *MMWR Morb Mortal Wkly Rep* 2013;62:901–2.
97. Schulte R, Jordan LC, Morad A, et al. Rise in late onset vitamin K deficiency bleeding in young infants because of omission or refusal of prophylaxis at birth. *Pediatr Neurol* 2014;50:564–8.
98. Hamrick HJ, Gable EK, Freeman EH, et al. Reasons for refusal of newborn vitamin K prophylaxis: implications for management and education. *Hosp Pediatr* 2016;6:15–21.