Increasing the dose of oral vitamin K prophylaxis and its effect on bleeding risk

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Abstract
Vitamin K prophylaxis in infancy aims to prevent life-threatening vitamin K deficiency bleeding (VKDB). The Dutch prophylactic oral daily regimen was increased sixfold from 25 to 150 μg because of a high failure rate. To evaluate the efficacy of this new regimen, incidences of intracranial VKDB under both regimens were compared using both general and targeted surveillance. Late VKDB in the general pediatric population was identified by the Netherlands Pediatric Surveillance Unit, between 1 October 2014 and 31 December 2016. Additionally, infants with intracranial vitamin K deficiency bleeding were identified using the Dutch Pediatric Intensive Care Evaluation registry. The incidence of intracranial VKDB as assessed by general and targeted surveillance decreased from 1.6 per 100,000 (95% CI, 0.4–5.1) to 1.3 per 100,000 (95% CI, 0.5–3.2) and from 3.1 per 100,000 live births (95% CI, 1.9–5.0) to 1.2 per 100,000 live births (95% CI, 0.6–2.3), respectively. Median time between consecutive cases in the latter increased from 24 to 154 days (p < 0.001).

Conclusion: A sixfold increase in oral vitamin K prophylaxis was associated with a surprisingly modest reduction in the incidence of intracranial VKDB, indicating that factors other than the dose need addressing to improve efficacy.

What is Known:
• The efficacy of intramuscular vitamin K prophylaxis is threatened by an increasing number of parents opting out.
• Oral prophylaxis represents an attractive and less invasive alternative but is inferior, especially in infants with malabsorption of vitamin K due to cholestasis.

What is New:
• Increasing the daily oral dose of vitamin K sixfold had a surprisingly modest effect on the incidence of late vitamin K deficiency bleeding.
• This finding indicates that factors other than the dose must play an important role.

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Keywords  Biliary atresia · Intracranial bleeding · Pediatric intensive care unit · Vitamin K prophylaxis · Vitamin K deficiency bleeding

Abbreviations

**IM** Intramuscular  
**NABI** Non-accidental brain injury  
**NSCK** Netherlands Pediatric Surveillance Unit  
**PFIC** Progressive familial intrahepatic cholestasis  
**PICE** Pediatric Intensive Care Evaluation  
**PICU** Pediatric intensive care unit  
**PIM2** Pediatric Index of Mortality 2  
**PIVKAs** Proteins induced in vitamin K absence  
**PT** Prothrombin time  
**VKD** Vitamin K deficiency  
**VKDB** Vitamin K deficiency bleeding

Introduction

Vitamin K prophylaxis in infancy aims to reduce the risk of vitamin K deficiency bleeding (VKDB), the consequences of which are potentially lethal [14]. Most countries have implemented vitamin K prophylactic regimens, but the route of administration, the dose, the dosing frequency, and the vitamin K formulation differ widely among regimens. The molecular form of vitamin K currently used in the Netherlands and nearly all countries for intramuscular (IM) and oral vitamin K prophylaxis is phylloquinone (vitamin K1). The efficacy of a single dose of 1 mg IM vitamin K1 is firmly established and is associated with a low risk of VKDB of < 0.2/100,000 newborns [12]. However, its efficacy at a population level is currently threatened by an increasing number of parents opting out [9, 10, 15, 16, 28]. On the other hand, a single dose of oral vitamin K1 prophylaxis—while as effective in preventing classical VKDB—is associated with a much higher risk of late VKDB (roughly 4–7/100,000) [27], which is predominantly manifested by intracranial hemorrhage [20].

The vast majority of prophylactic failures occur in breastfed infants with malabsorption of vitamin K, mostly due to cholestasis [17]. Unfortunately, malabsorption often only becomes apparent after bleeding has occurred. A prophylactic regimen should therefore allow protection for all infants, including those with unrecognized cholestatic liver disease.

By using targeted surveillance of infants with biliary atresia, it was previously shown that a weekly oral dose of 1 mg vitamin K offered a protection similar to IM administration in infants with cholestasis [23]. In contrast, a daily dose of 25 μg (0.175 mg weekly) was associated with a much higher risk in breastfed infants with biliary atresia and a much higher incidence of late VKDB of ~ 2.1 per 100,000 [23, 25]. To address this, the Dutch prophylactic dose was increased sixfold, from 25 daily to 150 μg daily (1.050 mg weekly) for all breastfed infants in February 2011 [4].

A recent study in patients with biliary atresia questioned the efficacy of this new regimen and suggested that the risk had remained unchanged [29]. The aim of this study is to determine the consequences of a sixfold increase in the oral prophylactic vitamin K dose (150 μg) on the overall incidence of late VKDB and late intracranial VKDB in the Netherlands in comparison with the former oral prophylactic dose of 25 μg.

Materials and methods

**General surveillance**

From 1 October 2014 to 31 December 2016, the Netherlands Pediatric Surveillance Unit (NSCK) of the Dutch Association for Pediatrics performed a nationwide active surveillance focused on the identification of infants with late VKDB.

**Patient selection**

Pediatricians were asked to report all infants in whom bleeding may have resulted from VKDB. Reported cases were confirmed as described previously [6]. Briefly, validation was performed using a questionnaire asking for information about the infant, feeding type, clinical presentation, dose and route of vitamin K prophylaxis, associated diseases, laboratory data, and outcome. Confirmed VKDB was diagnosed when prothrombin time (PT) was ≥ 4 times the control value and at least one of the following was present:

1. Platelet count normal or raised in combination with normal fibrinogen values
2. Prothrombin assay returned to normal after vitamin K administration
3. Concentration of PIVKAs (proteins induced in vitamin K absence) exceeding the normal controls [6]

**Incidence of late (intracranial) VKDB**

The incidence of late VKDB and late intracranial VKDB in the general pediatric population under the 150 μg regimen was calculated using these data (2014–2016) and was compared with the incidence under the 25 μg regimen by the NSCK in 2005 [6, 25].
Targeted surveillance

Infants with late intracranial VKDB were identified by using the Dutch Pediatric Intensive Care Evaluation (PICE) registry between 1 January 2008 and 31 December 2015. The diagnoses of all infants admitted to the eight Dutch pediatric intensive care units (PICUs) are registered in this national registry from 2003 onward.

Patient selection

All infants between the age of 8 days and 6 months who were admitted to a Dutch PICU with intracranial bleeding were identified in the PICE registry using the same procedure as previously described [25]. Briefly, the search strategy included search items that allowed detection through the diagnosis intracranial bleeding, through the symptoms of intracranial bleeding and through the underlying disorder. Search items were “brain dead,” “cerebral infarct or stroke,” “intracranial hemorrhage,” “convulsions,” “meningitis,” “gastro-intestinal bleeding,” “hepatitis,” “other liver diseases,” “biliary atresia,” “neonatal jaundice,” “other gastro-intestinal diseases,” and “coagulation defects” [25]. In case a center had not yet completed its PICE registration during the study period, an analogous in-house search was performed. Medical records of all selected patients were reviewed to identify infants with intracranial bleeding. Discharge letters and laboratory results were used to confirm vitamin K deficiency (VKD) as the cause of bleeding. Also, relevant clinical characteristics were obtained. Late intracranial VKDB was defined as intracranial bleeding confirmed by magnetic resonance imaging or computer tomography, in combination with a PT of ≥ 4 times the control value which normalized after vitamin K administration and/or a raised concentration of PIVKAs. A raised concentration of PIVKAs was defined as exceeding the normal controls [20]. Cases of “highly probable” intracranial bleeding, in combination with the above, were also considered to be late intracranial VKDB. Cases who were diagnosed with VKD before bleeding occurred were considered to be treatment failures.

Clinical characteristics

Infants with late intracranial VKDB were categorized into two groups according to the type of prophylaxis (25 μg vs. 150 μg). Vitamin K prophylaxis was considered to be given as recommended by the Dutch guideline at that time (1 mg at birth and 25 μg or 150 μg daily until the age of 3 months) unless otherwise specified. As the regimen was changed in February 2011, all patients with late intracranial VKDB who were born after February 2011 were considered to be 150-μg regimen cases. Age at diagnosis was defined as the age of the infant when first seen by a doctor with VKD-related symptoms.

Infants were classified as “exclusively breastfed” if they had received exclusively breastmilk from birth onward. Adequate vitamin K administration was defined as administration ≥ 5 times a week. Cholestasis was defined as a concentration of total serum bilirubin ≥ 50 μmol/l with a direct fraction of ≥ 20% [23]. Since the risk of VKDB is not correlated with the degree of conjugated hyperbilirubinemia [24], we also retrieved and described the total and conjugated bilirubin levels. To compare the severity of VKDB under the different regimens, the following parameters were determined: the Pediatric Index of Mortality 2 (PIM2) score, which can be used for comparison of risk-adjusted mortality among infants admitted to a PICU [18]; mechanical ventilation; length of stay at a PICU; neurosurgical intervention; occurrence of neurological sequelae; and mortality.

Incidence of late intracranial VKDB

The incidence of late intracranial VKDB between 2008 and 2015 was calculated using the number of live births for each year [1, 2].

Efficacy of the revised regimen

To evaluate the efficacy of the revised regimen, the time between events (median time between consecutive cases) under both regimens was compared, which is inversely related to the incidence. Additionally, we performed a sensitivity analysis by calculating the adjusted incidence of late intracranial VKDB, excluding infants who had received inadequate prophylaxis and infants that had not been exclusively breastfed. Approval for the study was obtained from the Medical Ethical Committee of the University Medical Center Utrecht.

Statistical analysis

Clinical and biochemical data were analyzed using a t test in case of a normal distribution and a Mann-Whitney U test for parameters with a non-normal distribution. A Pearson chi-squared test or Fisher’s exact test was used to determine statistical significance between groups in case of dichotomous parameters. A p value < 0.05 was considered statistically significant. SPSS (version 22.0; IBM Corp, Armonk, NY) was used for all analyses. The 95% confidence intervals for the incidences were calculated with R (version 3.3.65126.0_3-0) (supplementary information).
Results

General surveillance

Between 1 October 2014 and 31 December 2016, 10 cases with suspected late VKDB were reported to the NSCK. Of these, 1 infant was excluded from analysis because the prolonged coagulation time did not cause a bleeding. Of the remaining 9 cases, late intracranial VKDB was confirmed in 5 infants and suspected in 1 infant in whom PT was measured after parenteral administration of vitamin K. In the remaining 3 infants, bleeding occurred but at a different site (Table 1). One of these infants did not receive vitamin K administration and was therefore excluded from analysis. Under the 150-μg regimen, the incidence of confirmed late VKDB was 1.8 per 100,000 (95% CI, 0.8–3.9), more than 70% of which were intracranial bleedings, accumulating to an incidence of confirmed late intracranial VKDB of 1.3 per 100,000 (95% CI, 0.5–3.2). These incidences were lower than those obtained by the NSCK in 2005 under the 25-μg regimen: 3.2 per 100,000 (95% CI, 1.2–6.9) and 1.6 per 100,000 (95% CI, 0.4–5.1), respectively [6]. However, there are overlapping confidence intervals.

Targeted surveillance

Between 1 January 2008 and 31 December 2015, a total of 45,063 patients were admitted to the eight Dutch PICUs. Of these, 175 infants were diagnosed with intracranial bleeding. Proven or highly suspected non-accidental brain injury (NABI) represented the main cause (73 patients, 42%), followed by accidental head trauma (45 patients, 26%). Late intracranial VKDB was confirmed in 28 infants (16%). Patients with late intracranial VKDB presented significantly earlier than patients with intracranial bleeding due to NABI (50 days vs. 85 days, respectively, \( p < 0.001 \)).

| Sex; age (days) | Vitamin K prophylaxis | Clinical presentation | Late intracranial VKDB | Type of feeding | APTT(s)/PT(s)/INR | Underlying disorder | Outcome |
|----------------|------------------------|-----------------------|------------------------|-----------------|-------------------|-------------------|---------|
| M; 22          | 1 mg postpartum, 150 μg/day per os | Intracranial bleeding | Yes | BF | > 200/180/NM | AATD | Died |
| M; 52          | Since 10 days postpartum 150 μg/day per os | Intracranial bleeding | Yes | BF | > 200/180/NM | Unknown | Epilepsy |
| F; 72          | 1 mg postpartum, 150 μg/day per os | Intracranial, nasal, and gastro-intestinal bleeding, hematomas | Yes | BF | > 150/18/NM | PFIC type 2 | Died |
| F; 37          | 1 mg postpartum, 150 μg/day per os | Intracranial bleeding | Yes | BF | 58/39.9/3.92* | Biliary atresia | Died |
| M; 38          | 1 mg postpartum, 150 μg/day per os | Intracranial and gastro-intestinal bleeding | Yes | BF | 120/120/NM | Unknown | No sequelae |
| F; 21          | 1 mg postpartum, 150 μg/day per os | Intracranial bleeding | Yes | BF | > 180/90/NM | Suspected PFIC | Full recovery |
| F; 45          | 1 mg postpartum, 150 μg/day per os | Hematomas chest and hand | No | BF | > 200/10/NM | Biliary atresia | Full recovery |
| M; 19          | 1 mg postpartum, 150 μg/day per os | Umbilical bleeding | No | BF | > 180/180/NM | AATD | Unknown |
| M; 17          | No administration | Gastro-intestinal bleeding | No | BF | 152/147/NM | None | Unknown |

\( M \) male, \( F \) female, \( BF \) breastfeeding, \( APTT \) activated partial thromboplastin time, \( PT \) prothrombin time, \( INR \) international normalized ratio, \( NM \) not measured, \( AATD \) alpha-1 antitrypsin deficiency, \( PFIC \) progressive familial intrahepatic cholestasis

*Measured after vitamin K administration
there was a significant difference between the intracranial localization of hematomas in infants with VKDB and in infants with bleeding due to NABI: the latter group presented primarily with subdural hematomas whereas VKDB predominantly manifested as a combination of subdural and intracerebral bleeding ($p = 0.020$).

**Late intracranial VKDB**

Under the 25-µg regimen (January 2008–February 2011; 38 months), late intracranial VKDB was confirmed in 18 infants and suspected in 2 additional infants in whom diagnosis could not be confirmed as PT was measured after vitamin K supplementation had been introduced. Under the 150-µg regimen (March 2011–December 2015; 58 months), late intracranial VKDB was confirmed in 10 infants (Table 2). Clinical and biochemical characteristics of infants with confirmed late intracranial VKDB are listed in Table 3. Under the 25-µg regimen, all infants were exclusively breastfed. In all 16 infants in which bilirubin values were available, both the total and direct fractions were raised, suggesting suboptimal bile flow. Of these, 14 infants met the previously described criteria of cholestasis. An underlying disorder predisposing to cholestasis was identified in 7 infants: biliary atresia (4), α-1 antitrypsin deficiency, PFIC, and Zellweger syndrome (1 each). Two infants had received inadequate vitamin K administration.

**Incidence of late intracranial VKDB**

The annual incidence of late intracranial VKDB under the former regimen of 25 µg vitamin K ranged from 1.6 per 100,000 live births (95% CI, 0.4–5.2) to 4.9 per 100,000 live births (95% CI, 2.4–9.6), with an average incidence of 3.1 per 100,000 live births (95% CI, 1.9–5.0). When infants with suspected VKDB were included in the analysis, the average incidence was 3.4 per 100,000 live births (95% CI, 2.2–5.4). After implementation of the 150-µg regimen, the annual incidence of late intracranial VKDB ranged from 0.6 per 100,000 live births (95% CI, 0.0–3.7) to 1.8 per 100,000 live births (95% CI, 0.5–5.6), with an average incidence of late intracranial VKDB of 1.2 per 100,000 live births (95% CI, 0.6–2.3) (Table 4).

| Table 2 | Causes of intracranial bleeding in infants between the age of 8 days and 6 months admitted to a Dutch PICU between 2008 and 2015 under two different vitamin K oral prophylactic regimens |
|---------|----------------------------------------------------------------------------------------------------------------------|
| Cause                                          | 25 µg: January 2008–February 2011 Number (%) | 150 µg: March 2011–December 2015 Number (%) | $p$ value |
| Non-accidental brain injury                     | 39 (44)                                         | 34 (39)                                         | 0.482    |
| Vitamin K deficiency                            | 20 (23)                                         | 10 (12)                                         | 0.041    |
| Confirmed                                       | 18 (21)                                         | 10 (12)                                         | 0.092    |
| Accidental head trauma                          | 19 (22)                                         | 26 (30)                                         | 0.244    |
| Other coagulation disorders                     | 1 (1)                                           | 3 (3)                                           | 0.621    |
| Iatrogenous                                     | 2 (2)                                           | 2 (2)                                           | 1.000    |
| Unknown                                         | 1 (1)                                           | 4 (5)                                           | 0.368    |
| Vascular malformation                           | 1 (1)                                           | 3 (3)                                           | 0.621    |
| Due to menigitis                                | 1 (1)                                           | 3 (3)                                           | 0.621    |
| Due to disseminated intravascular coagulation   | 2 (2)                                           | 0 (0)                                           | 0.246    |
| Secondary to sinus thrombosis                   | 1 (1)                                           | 1 (1)                                           | 0.000    |
| Birth trauma                                    | 1 (1)                                           | 0 (0)                                           | 0.497    |
| Genetic collagen disorder                       | 0 (0)                                           | 1 (1)                                           | 1.000    |
| Total                                           | 88                                              | 87                                              |          |
As a consequence, the median time between consecutive cases increased significantly after the introduction of this regimen, from 24 under the 25-μg regimen to 154 days under the 150-μg regimen \((p < 0.001)\). (Fig. 1a, b).

**Sensitivity analysis**

When excluding infants who had received inadequate prophylaxis (4 and 2 infants for the 25-μg and 150-μg regimens, respectively) and infants who developed intracranial VKDB due to treatment failure (1 infant for the 150-μg regimen), the adjusted incidence of late intracranial VKDB under the 25-μg regimen was calculated as 2.4 per 100,000 live births (95% CI, 1.4–4.1). The adjusted incidence under the 150-μg regimen was calculated as 0.8 per 100,000 live births (95% CI, 0.4–1.8).

### Discussion

In this study, we exploited two independent nationwide surveillance strategies to determine the effect of a six-fold dose increase of oral vitamin K prophylaxis on the incidence of intracranial hemorrhages due to VKD and showed that the incidence of late intracranial VKDB was modestly reduced after introduction of the revised regimen. However, the protection obtained by this six-fold dose increase is limited in comparison with the excellent protection offered by a single dose of IM vitamin K after birth [12] and is unexpectedly lower than a regimen previously used in Denmark with the same cumulative weekly dose of vitamin K [23]. This discrepancy strongly suggests that factors other than the dose must play an important role. Compliance issues with the daily regimen might contribute to poor protection; however, this was the case in only 2 infants for the revised regimen, and previous investigations indicate compliance is generally adequate [21]. Improved
Fractional absorption of one larger dosage compared with multiple smaller dosages has been suggested, although evidence is currently lacking [29]. Alternatively, the formulation in which vitamin K is administered could be an explanation. Dutch oral vitamin K is dissolved in arachid oil, the hydrophobic nature of which is likely to impede absorption in infants with suboptimal bile flow. In several countries with oral vitamin K regimens, vitamin K is administered through Konakion® mixed micelles (MM) which more closely resembles the situation in the gut. However, even this formulation does not fully prevent VKDB in infants with cholestasis due to impaired intestinal absorption [26], likely due to micellar decomposition in the stomach as a consequence of low pH [22]. A recent study describes a new formulation of vitamin K prophylaxis which circumvents gastric micellar decomposition and therefore might be a promising oral form of prophylaxis for infants with suboptimal bile flow [19].

The present study underlines the usefulness of pediatric intensive care registries in assessing the efficacy of national regimens of vitamin K prophylaxis. First, this study confirms that this targeted approach is associated with higher retrieval rates as compared with general surveillance studies [25]. Higher retrieval decreases the risk that differences in calculated incidences are due to variations in retrieval rate rather than changes in the true incidence. It is important to take the higher retrieval rate, thus higher incidences, into account when comparing incidences obtained using targeted surveillance with those obtained using general surveillance. Second, the detailed information regarding timing of events allowed us to calculate the time between events [19].

Vitamin K prophylaxis

Incidence of intracranial bleeding and late intracranial VKDB in the Netherlands between 2008 and 2015 under the 25 µg and 150 µg oral prophylactic regimen

| Vitamin K prophylaxis | 25 µg | 150 µg |
|-----------------------|-------|-------|
| **Year** | **2008** | **2009** | **2010** | **Jan-Feb 2011** | **Total** | **March-Dec 2011** | **2012** | **2013** | **2014** | **2015** | **Total** |
| Live births (N) | 184,634 | 184,915 | 184,397 | 29,231 | 583,117 | 150,829 | 175,999 | 171,341 | 175,181 | 170,510 | 843,820 |
| Patients admitted to a PICU(N) | 4383 | 5205 | 5518 | 965 | 16,519 | 4775 | 6014 | 5897 | 5881 | 5977 | 28,544 |
| Intracranial bleeding (N) | 22 | 31 | 29 | 3 | 85 | 9 | 21 | 12 | 22 | 26 | 90 |
| Incidence of intracranial bleeding per 100,000 (95% CI) | 11.9 (7.7–18.4) | 16.8 (11.6–24.1) | 15.7 (10.7–22.9) | 16.0 (11.7–21.3) | 14.6 (11.7–18.1) | 6.0 (2.9–11.8) | 11.9 (7.6–18.6) | 7.0 (3.8–12.6) | 12.6 (8.1–19.4) | 15.2 (10.2–22.7) | 10.7 (8.6–13.2) |
| Late intracranial VKDB (N) | 4 | 3 | 9 | 2 | 18 | 2 | 1 | 3 | 2 | 10 |
| Incidence of late intracranial VKDB per 100,000 (95% CI) | 2.2 (0.7–6.0) | 1.6 (0.4–5.2) | 4.9 (2.4–9.6) | 6.8 (1.2–27.6) | 3.1 (1.9–5.0) | 1.3 (0.2–5.3) | 0.6 (0.0–3.7) | 1.8 (0.5–5.6) | 1.1 (0.2–4.6) | 1.2 (0.2–4.7) | 1.2 (0.6–2.3) |

PICU: pediatric intensive care unit, VKDB: vitamin K deficiency bleeding

*3 infants with intracranial bleeding due to other causes than VKD were born before the new prophylaxis was introduced and were therefore included in the 25-µg prophylaxis group in Table 2.
of late VKDB (1.3 and 1.5 per 100,000 in Germany and Australia, respectively, for the years 1993 and 1994). An oral dosing regimen of 2 × 2 mg vitamin K in Switzerland resulted in an incidence of 1.2 per 100,000 for 1995–2002. For a dosing regimen of 3 × 2 mg, incidences varied from 0.4 to 0.8 per 100,000 in 1995–2001 (Germany), 0.43 per 100,000 (UK), and 0.87 per 100,000 since 2003 (Switzerland). The lowest incidence of late VKDB under oral vitamin K prophylaxis has been described in Denmark: 0.0 per 100,000 in 1992–2000 (2 mg vitamin K at birth, followed by 1 mg weekly for 3 months). However, Denmark switched to IM vitamin K administration in 2000 due to a lack of a licensed product. For countries with IM prophylaxis, lower incidences of 0.37 per 100,000 (Canada), 0.16 per 100,000 (New Zealand), and 0.1 per 100,000 (UK, 1 mg IM vitamin K at birth, 3 × 1 mg orally) have been described [11, 12]. Based on this superior efficacy, the NICE guidelines of 2015 recommend IM vitamin K prophylaxis for all newborns to prevent VKDB [13].

Despite its efficacy, IM administration of vitamin K increasingly encounters resistance from parents [9]. Reasons for concern include exposure of the baby to toxic ingredients, excessive dose and side effects, the fear of an, although not substantiated [7], association with cancer, and the painful injections. Inadequate information during the antenatal period about the importance of vitamin K prophylaxis can also be a reason for refusal: parents consider vitamin K unphysiological and therefore gratuitous in uncomplicated birth [16, 28]. Risk factors for parental refusal of IM vitamin K administration were previously described [9, 15]. Vitamin K refusal was more likely to be associated with planned home delivery and midwife-assisted deliveries than hospital delivery and delivery by a physician. In the Netherlands, a substantial part of newborns is delivered at home (18.4% vs. 80.7% in a hospital vs. 0.9% elsewhere) [3] and could consequently be at risk of parental IM vitamin K refusal. Proper counseling, especially during the antenatal period, is therefore of great importance. If parents persist and refuse to have their child injected, the Dutch Health Council presently recommends an oral alternative, namely, 3 doses of 2 mg vitamin K (at birth, after 4–6 days and 4–6 weeks) for breastfed infants [5], based on a Swiss study [8]. The NICE guidelines also recommend oral vitamin K as a second-line option in case of parental decline, although dose and dosage frequency are not specified [13].

There are some limitations to this study. It is possible that some cases with intracranial VKDB were not admitted to the PICU in case of few symptoms, or died elsewhere and therefore remained unreported. Furthermore, earlier detection of cholestatic liver disease, including biliary atresia, may theoretically decrease the incidence of late VKDB, as these infants are treated with higher vitamin K dosages once diagnosed. However, since there has been no change in the number of registered patients with biliary atresia or the age at diagnosis after introduction of the revised regimen [29], this is not likely to have influenced the results. Finally, targeted surveillance within relevant subpopulations requires the existence of national registries. This in turn demands a substantial and ongoing effort, the importance of which cannot easily be overstated.

In conclusion, a sixfold increase in the oral prophylactic vitamin K dose—from 25 to 150 μg daily—resulted in a significant but relatively modest reduction in the incidence of late intracranial VKDB. However, this protection compares poorly to the efficacy of IM
vitamin K prophylaxis, indicating that factors other than the dose should be addressed to further improve oral vitamin K prophylactic regimens.

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Authors’ contributions Yvette N. Löwensteyn carried out the initial analyses and drafted the initial manuscript.

Nicolaas J.G. Jansen designed the study, coordinated and supervised data collection, and reviewed and revised the manuscript.

Peter M. van Hasselt conceptualized and designed the study, supervised data collection, and reviewed and revised the manuscript.

Members of the Dutch PICE/SKIC working group accommodated data collection and reviewed the manuscript.

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

Compliance with ethical statements Approval for the study was obtained from the Medical Ethical Committee of the University Medical Center Utrecht.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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