Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries

Peter M. van Hasselt, Tom J. de Koning, Nina Kvist, Elseemieke de Vries, Christina Rydahl Lundin, Ruud Berger, Jan L. L. Kimpen, Roderick H. J. Houwen, Marianne Horby Jørgensen and Henkjan J. Verkade

_Pediatrics_ 2008;121:e857
DOI: 10.1542/peds.2007-1788

The online version of this article, along with updated information and services, is located on the World Wide Web at:

[http://pediatrics.aappublications.org/content/121/4/e857.full.html](http://pediatrics.aappublications.org/content/121/4/e857.full.html)
Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries

Peter M. van Hasselt, MD*, Tom J. de Koning, MD, PhD*, Nina Kivist, MD*, Elsemiek de Vries, BS5, Christina Rydahl Lundin, BS4, Ruud Berger, MD, PhD*, Jan L. L. Kimpen, MD, PhD*, Roderick H. J. Houwen, MD, PhD*, Marianne Horby Jorgensen, MD, PhD*, Henkjan J. Verkade, MD, PhD*, and the Netherlands Study Group for Biliary Atresia Registry

*Department of Pediatrics, Wilhelmina Children’s Hospital, and Laboratory for Metabolic Diseases, University Medical Center Utrecht, Utrecht, Netherlands; Departments of Pediatric Surgery and Pediatrics, University Hospital of Copenhagen, Copenhagen, Denmark; Department of Pediatrics, University Medical Center Groningen, Groningen, Netherlands.

The authors have indicated they have no financial relationships relevant to this article to disclose.

**What’s Known on This Subject**
- Intramuscular vitamin K prophylaxis at birth efficaciously prevents vitamin K deficiency bleeding in infancy but increasingly encounters parental refusal. We investigated whether frequent oral prophylaxis prevents vitamin K deficiency bleeding by assessing its prevalence in infants with still-unrecognized cholestatic liver disease.

**What This Study Adds**
- In breastfed infants with cholestatic liver disease, weekly oral (1-mg) vitamin K prophylaxis and intramuscular prophylaxis effectively prevented vitamin K deficiency bleeding. In contrast, daily oral prophylaxis (25 μg) was associated with frequent (>90%) and severe vitamin K deficiency bleeding.

**ABSTRACT**

OBJECTIVE. Newborns routinely receive vitamin K to prevent vitamin K deficiency bleeding. The efficacy of oral vitamin K administration may be compromised in infants with unrecognized cholestasis. We aimed to compare the risk of vitamin K deficiency bleeding under different prophylactic regimens in infants with biliary atresia.

PATIENTS AND METHODS. From Dutch and Danish national biliary atresia registries, we retrieved infants who were either breastfed and received 1 mg of oral vitamin K at birth followed by 25 μg of daily oral vitamin K prophylaxis (Netherlands, 1991–2003), 2 mg of oral vitamin K at birth followed by 1 mg of weekly oral prophylaxis (Denmark, 1994 to May 2000), or 2 mg of intramuscular prophylaxis at birth (Denmark, June 2000–2005) or were fed by formula. We determined the absolute and relative risk of severe vitamin K deficiency and vitamin K deficiency bleeding on diagnosis in breastfed infants on each prophylactic regimen and in formula-fed infants.

RESULTS. Vitamin K deficiency bleeding was noted in 25 of 30 of breastfed infants on 25 μg of daily oral prophylaxis, in 1 of 13 on 1 mg of weekly oral prophylaxis, in 1 of 10 receiving 2 mg of intramuscular prophylaxis at birth, and in 1 of 98 formula-fed infants (P < .001). The relative risk of a bleeding in breastfed compared with formula-fed infants was 77.5 for 25 μg of daily oral prophylaxis, 7.2 for 1 mg of weekly oral prophylaxis, and 9.3 for 2 mg of intramuscular prophylaxis at birth.

CONCLUSIONS. A daily dose of 25 μg of vitamin K fails to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. One milligram of weekly oral prophylaxis offers significantly higher protection to these infants and is of similar efficacy as 2 mg of intramuscular prophylaxis at birth. Our data underline the fact that event analysis in specific populations at risk can help to evaluate and improve nationwide prophylactic regimens.
artificially fortified and contain \( \sim 50 \mu g/L \). A variety of prophylactic regimens have been introduced to prevent VKDB in breastfed infants.\textsuperscript{7–10} A single intramuscular dose of vitamin K at birth is considered most efficacious, reducing the incidence of classical, as well as late, VKDB to \(<0.2\) per 100 000, although recent evidence suggests that effectiveness may be hampered by a higher risk of omission of prophylaxis.\textsuperscript{10–12} Oral administration of vitamin K at birth prevents classical VKDB but fails to prevent late VKDB, even when administered in very high dosages.\textsuperscript{13} Based on these observations, breastfed infants on oral prophylaxis receive additional doses of vitamin K in the first months of life.\textsuperscript{12} This strategy has substantially reduced the incidence of late VKDB.\textsuperscript{12–14} However, prophylactic failures have continued to occur, mostly in infants who later proved to have a cholestatic liver disease.\textsuperscript{3,9,15–18}

Cholestatic infants are especially sensitive to suboptimal vitamin K availability, because the absence of intestinal bile greatly reduces the absorption of vitamin K and other fat-soluble vitamins.\textsuperscript{19,20} The repeated occurrence of prophylactic failures in infants with unrecognized cholestatic liver disease warrants careful evaluation of the efficacy of vitamin K prophylactic regimens in these infants. National registries for biliary atresia provide a unique opportunity to quantitate the efficacy of vitamin K prophylaxis in a well-defined and homogeneous population of cholestatic infants. These registries allow us to determine the absolute risk of VKDB in breastfed infants under different prophylactic regimens. Moreover, these risks can be weighed against the risk in formula-fed infants. We performed a retrospective cohort study in Dutch and Danish infants with biliary atresia to compare the efficacy of frequent (daily or weekly) oral vitamin K prophylaxis with intramuscular (IM) vitamin K prophylaxis at birth.

**METHODS**

**Study Population**

Data from Dutch biliary atresia patients born between 1991 and 2003 were obtained from the Netherlands Study Group for Biliary Atresia Registry, a joint effort of the Dutch Society for Pediatrics and the Dutch Society for Pediatric Surgery. Danish biliary atresia patients born between 1994 and 2005 were retrieved from the University Hospital of Copenhagen (Rigs Hospital) Department of Pediatric Surgery. The Rigs Hospital is the Danish national referral center for patients with suspected biliary atresia and for Kasai hepatportoenterostomy.

Routine vitamin K prophylaxis aims to prevent VKDB in apparently healthy term infants. Infants with a gestational age of \(<37\) weeks or a birth weight of \(<2000\) g were excluded, because these infants routinely receive additional vitamin K prophylaxis. Patients hospitalized from birth until diagnosis were also excluded, because they may have received additional vitamin supplements, as well as other diets. Late VKDB has been defined to occur after the first week of life and before the age of 6 months.\textsuperscript{3} Accordingly, infants were excluded if cholesta-
PT\textsubscript{patient}:PT\textsubscript{control}. If a PT\textsubscript{control} was not determined by the laboratory, it was defined as the mean of the provided reference range.

VKD was defined as a PR of >1.5 in combination with a normal thrombocyte count. A PR above this threshold is rare in healthy infants after the first week of life.\textsuperscript{22,23} Significant PR elevations in otherwise healthy biliary atresia infants are unlikely to be because of other causes.\textsuperscript{24} A PR of >4 was designated as “severe” VKD. VKDB was defined as bruising, bleeding, or intracranial hemorrhage in combination with a PR of >4 in any infant between 8 days and 6 months of age and normalizing after administration of vitamin K.\textsuperscript{2} The number of bleedings and their locations were noted.

Statistical Analysis
We performed a 2-way analysis of variance of clinical and biochemical parameters with a normal distribution pattern to test for statistical differences between groups. Kruskal-Wallis analysis was used for those parameters with a nonnormal distribution. In case statistical significant differences were found, a Bonferroni test for multiple comparisons or a Mann-Whitney U test was used for posthoc analysis, respectively. Fisher’s exact test was performed to determine statistical significance between groups in case of dichotomous parameters. The relative risks (RRs) and 95% confidence intervals (CIs) for VKDB and biochemical levels of VKD were calculated.

We performed conditional logistic regression analysis to assess potential confounding. First, all of the clinical and biochemical parameters were considered as possible confounders and included, 1 by 1, as covariates. Risk factors that changed the odds ratio (OR) by >10% were added to a model and were maintained in the final model if they induced a change of >10% in that model. SPSS 12.01 (SPSS Inc, Chicago, IL) was used for all of the analyses.

RESULTS
Between January 1991 and December 2003, 139 biliary atresia patients were included into the Netherlands Study Group of Biliary Atresia Registry (Table 1). Seventeen of these infants did not meet the inclusion criteria; 9 had stayed in a hospital from birth until diagnosis, 7 were born outside of the Netherlands, and 1 was excluded because of prematurity. Thirty (25%) of the remaining 122 infants were exclusively breastfed, and 88 (72%) were formula fed. In 4 infants, the type of feeding was not documented. In total, 63% of all of the infants received any amount of breastfeeding, which is similar to the 51% to 63% of infants using breastfeeding at the age of 6 weeks in the Netherlands from 1991 to 2003, as known from epidemiologic data (www.cbs.nl/statline).

A total of 46 patients born between January 1994 and December 2005 were reported to the Danish Biliary Atresia Registry. Nine infants were excluded; 6 had stayed in a hospital from birth until diagnosis and 3 were excluded because of prematurity. In addition, 5 infants born before June 2000 were excluded because vitamin K was administered IM after a complicated delivery. Twenty three of the remaining 32 infants (77%) were breastfed, of which 13 were born before June 2000.

Clinical Characteristics
Infants from both countries were categorized according to the type of prophylaxis that they received. Table 2 summarizes the clinical characteristics in breastfed infants on frequent (daily or weekly) oral or IM prophylaxis and the combined group of formula-fed infants. Overall, breastfed infants had a slightly, but significantly, higher birth weight than formula-fed infants. Cholestasis was found ~14 days earlier in Dutch breastfed infants compared with formula-fed infants (P < .001). The age at diagnosis correlated significantly with parameters of cholestatic liver disease.
VKD in Breastfed Infants

VKD was evident in all (30 of 30) Dutch breastfed infants with biliary atresia (Table 3). VKD was severe in 29 of 30 (96%), and this was associated with a VKDB in 25 of 30 (83%). Fifteen infants (50%) had multiple bleedings. An intracranial hemorrhage was diagnosed in 13 of 30 (43%) Dutch breastfed infants. In contrast, VKDB occurred in only 1 of the Danish infants after weekly oral prophylaxis (1 of 13 [8%]) and also in 1 after IM prophylaxis (1 of 10 [10%]; each prophylaxis [1 of 13 [8%]) and also in 1 after IM prophylaxis (1 of 13 [10%]; each prophylaxis)...

Efficacy of Vitamin K Prophylaxis in Breastfed Infants: Comparison With Formula Feeding

We compared the risk of (severe) VKD and VKDB in breastfed infants receiving frequent oral or IM prophylaxis with the risk in formula-fed infants (Table 4). Only 1 of the 93 formula-fed infants had a VKDB. Dutch breastfed infants were poorly protected against VKDB compared with formula-fed infants, with a relative risk for a VKDB of 27.5 (95% CI: 11.0–548.0). Similar results were obtained when only Dutch formula-fed infants were used for comparison (RR: 73.3; 95% CI: 10.4–518.0).

Comparison With Formula Feeding

Our data show that the Dutch vitamin K prophylactic regimen does not protect breastfed infants with biliary atresia. More than 80% of these infants had developed a VKDB at the time that cholestasis was diagnosed. The clinical significance of this is illustrated by the fact that 43% of breastfed infants with biliary atresia presented during the first 4 weeks of life and 60% during the first 12 weeks.

DISCUSSION

Our data show that the Dutch vitamin K prophylactic regimen does not protect breastfed infants with biliary atresia. More than 80% of these infants had developed a VKDB at the time that cholestasis was diagnosed. The clinical significance of this is illustrated by the fact that 43% of breastfed infants with biliary atresia presented during the first 4 weeks of life and 60% during the first 12 weeks.

Data show infants with biliary atresia. All of the infants in the first 3 columns were exclusively breastfed. ASAT indicates aspartate aminotransferase; ALAT, Alanine aminotransferase.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>25 μg Daily Oral (n = 30)</th>
<th>1 mg Weekly Oral (n = 13)</th>
<th>2 mg IM at Birth (n = 10)</th>
<th>Formula Fed (n = 93)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)a</td>
<td>10 (33)</td>
<td>7 (54)</td>
<td>6 (60)</td>
<td>49 (53)</td>
<td>.260</td>
</tr>
<tr>
<td>Birth weight, mean ± SD, gb</td>
<td>3351 ± 404</td>
<td>3517 ± 347</td>
<td>3304 ± 525</td>
<td>3115 ± 629</td>
<td>.050</td>
</tr>
<tr>
<td>Age at diagnosis, median (interquartile range), d</td>
<td>35 (28–43)</td>
<td>46 (26–59)</td>
<td>54 (14–70)</td>
<td>49 (38–61)</td>
<td>.001</td>
</tr>
<tr>
<td>Weight at diagnosis, mean ± SD, g</td>
<td>3959 ± 423</td>
<td>4531 ± 922</td>
<td>4576 ± 1186</td>
<td>4150 ± 845</td>
<td>.080</td>
</tr>
<tr>
<td>Bilirubin total, median (interquartile range), μmol/Lc</td>
<td>147 (104–202)</td>
<td>153 (97–289)</td>
<td>197 (140–304)</td>
<td>178 (122–257)</td>
<td>.080</td>
</tr>
<tr>
<td>Bilirubin direct, median (interquartile range), μmol/Lc</td>
<td>98 (71–135)</td>
<td>124 (85–193)</td>
<td>135 (82–182)</td>
<td>127 (93–176)</td>
<td>.130</td>
</tr>
<tr>
<td>Bilirubin indirect, median (interquartile range), μmol/Lc</td>
<td>41 (27–76)</td>
<td>193 (152–233)</td>
<td>181 (125–237)</td>
<td>154 (125–180)</td>
<td>.090</td>
</tr>
<tr>
<td>ASAT, median (interquartile range), U/Lc</td>
<td>144 (94–235)</td>
<td>131 (103–154)</td>
<td>86 (63–150)</td>
<td>104 (84–133)</td>
<td>.420</td>
</tr>
<tr>
<td>ALAT, median (interquartile range), U/Lc</td>
<td>88 (66–135)</td>
<td>52 (34–111)</td>
<td>49 (43–88)</td>
<td>37 (25–62)</td>
<td>.080</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>25 μg Daily Oral, n/N (%)</th>
<th>1 mg Weekly Oral, n/N (%)</th>
<th>2 mg IM at Birth, n/N (%)</th>
<th>Daily Versus Weekly Oral</th>
<th>Daily Oral Versus IM at Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>VKD</td>
<td>30/30 (100)</td>
<td>5/13 (39)</td>
<td>3/10 (30)</td>
<td>&lt;.001</td>
<td>2.6</td>
</tr>
<tr>
<td>Severe VKD</td>
<td>29/30 (97)</td>
<td>3/13 (23)</td>
<td>2/10 (20)</td>
<td>&lt;.001</td>
<td>4.2</td>
</tr>
<tr>
<td>VKDB</td>
<td>25/30 (83)</td>
<td>1/13 (8)</td>
<td>1/10 (10)</td>
<td>&lt;.001</td>
<td>10.8</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>13/30 (43)</td>
<td>0/13 (0)</td>
<td>0/10 (0)</td>
<td>&lt;.001</td>
<td>b</td>
</tr>
</tbody>
</table>

a VKD was defined by a normal thrombocyte count and PR of >1.5, severe VKD by a PR of >4.

b Data cannot be computed. P = 1.0 for all of the comparisons between weekly oral and IM prophylaxis.

f This value was determined by using the Kruskal-Wallis test.

g This value was determined by using ANOVA.

h This value was determined by using Fisher’s exact test.
with an intracranial hemorrhage. The risk of VKDB in Dutch breastfed infants with biliary atresia was 8 to 10 times higher than in breastfed infants on either weekly oral prophylaxis or IM prophylaxis at birth and ~80 times higher than in formula-fed infants.

The design of the present study was set out to minimize the risk of bias. To reduce selection bias, we focused on infants with biliary atresia, a rarely missed diagnosis for which national registries are available. The incidence of biliary atresia in the Netherlands and Denmark, calculated from our present study, was 1:21 321 and 1:17 329, respectively. These incidences are in close agreement with surveillance data from the Netherlands under the same prophylactic regimen. The risk in formula-fed infants was used to compare the risk in breastfed infants under the 3 prophylactic regimens.

Our definition of a VKD was based on an elevated PR in the absence of thrombocytopenia, parallel to the case definition of VKDB. Although this definition largely excludes diffuse intravascular coagulation, it does not exclude other causes of PR elevation and may, therefore, give rise to misclassification. However, we do not consider this a major concern in the context of infants with biliary atresia, a condition characterized by poor vitamin K absorption. Moreover, liver dysfunction in biliary atresia is unlikely to cause a PR of >1.5 during the first months of life. Similarly, a "physiologic" PR of >1.5 is rare after the first week of life. We also analyzed the data using a higher cutoff value of the PR (>2), but the results were essentially identical (Table 4).

The observed failure of the current Dutch regimen to protect breastfed biliary atresia infants contrasts with surveillance data obtained after introduction of this regimen. These surveillance data indicate that daily oral vitamin K prophylaxis was of similar efficacy as IM prophylaxis. This conclusion was supported by the observation that Dutch breastfed infants had adequate vitamin K levels throughout the first 3 months of life and that their coagulation parameters remained within normal limits. However, these studies focused on healthy infants and did not address the efficacy of vitamin K prophylaxis in conditions with poor absorption of vitamin K, such as preterm infants, to reduce the risk of misclassification. Although some clinical parameters differed significantly between groups, these parameters did not significantly influence the risk of VKDB in breastfed infants on conditional logistic regression analysis.

Our definition of a VKD was based on an elevated PR compared with a normal thrombocyte count and a PR of >1.5, severe VKD by a PR of >3.

In the absence of thrombocytopenia, parallel to the case definition of VKDB. Although this definition largely excludes diffuse intravascular coagulation, it does not exclude other causes of PR elevation and may, therefore, give rise to misclassification. However, we do not consider this a major concern in the context of infants with biliary atresia, a condition characterized by poor vitamin K absorption. Moreover, liver dysfunction in biliary atresia is unlikely to cause a PR of >1.5 during the first months of life. Similarly, a "physiologic" PR of >1.5 is rare after the first week of life. We also analyzed the data using a higher cutoff value of the PR (>2), but the results were essentially identical (Table 4).

The observed failure of the current Dutch regimen to protect breastfed biliary atresia infants contrasts with surveillance data obtained after introduction of this regimen. These surveillance data indicate that daily oral vitamin K prophylaxis was of similar efficacy as IM prophylaxis. This conclusion was supported by the observation that Dutch breastfed infants had adequate vitamin K levels throughout the first 3 months of life and that their coagulation parameters remained within normal limits. However, these studies focused on healthy infants and did not address the efficacy of vitamin K prophylaxis in conditions with poor absorption of vitamin K, such as those observed in cholestatic infants. This approach may give rise to equivocal results: recent surveillance data from the Netherlands under the same prophylactic regimen seem to contradict the previous findings, with a reported incidence of 3:100 000. Five of 6 reported failures had an unrecognized cholestatic liver disease.

Reliable information on the efficacy of prophylactic regimens in high-risk infants is of increasing importance, because these infants now represent the vast majority of prophylactic failures. The method presented here, comparison of well-delineated and homogeneous risk populations, may be very helpful in this respect. In contrast to nationwide surveillance studies, which are sensitive to underreporting, it seems to be a reliable method to detect prophylactic failures. The presently applied method not only allows us to determine the number of failures but also to calculate the failure rate, because clinical information can be obtained from all of the infants within such a

### TABLE 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>VKD*</th>
<th>95% CI</th>
<th>Severe VKD</th>
<th>95% CI</th>
<th>VKDB</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula fed (n = 93)</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Breastfed +2 mg IM at birth (n = 10)</td>
<td>4.7</td>
<td>1.4–15.8</td>
<td>18.6</td>
<td>1.9–187.0</td>
<td>9.3</td>
<td>0.6–138.0</td>
</tr>
<tr>
<td>Breastfed +1 mg weekly oral (n = 13)</td>
<td>6.0</td>
<td>2.1–16.8</td>
<td>21.5</td>
<td>2.4–1910</td>
<td>7.2</td>
<td>0.5–108.0</td>
</tr>
<tr>
<td>Breastfed +25 μg daily oral (n = 30)</td>
<td>15.5</td>
<td>7.2–33.6</td>
<td>89.9</td>
<td>12.7–6320</td>
<td>77.5</td>
<td>11.0–548.0</td>
</tr>
</tbody>
</table>

NA indicates not applicable. VKD was defined by a normal thrombocyte count and a PR of <1.5, severe VKDB by a PR of >3.

a Similar results were found when a PR of >2 was chosen to define VKD. b It was 6.2 (95% CI: 1.2–32.8), for weekly oral prophylaxis it was 9.5 (95% CI: 2.4–37.9), and for daily oral prophylaxis it was 31 (95% CI: 10.2–94.4).

b Dutch and Danish formula-fed infants with biliary atresia receiving oral (not IM) prophylaxis were combined. VKD was found in 1 of 93, severe VKD in 1 of 93, and VKDB in 6 of 93 of these infants.

c Values as determined by using Fisher’s exact test were .04 for VKD, .02 for severe VKD, and .19 for VKDB.

d Values were .004 for VKD, .005 for severe VKD, and .23 for VKDB.
population. It also enables a comparison of failure rates between different subpopulations, such as breastfed infants. Moreover, the availability of biochemical parameters can be used to establish the risk of a “near miss,” (eg, a severe VKD diagnosed before a bleeding could develop). Most importantly, as presently shown, this strategy allows the detection of differences between regimens in their ability to protect high-risk populations, which remained undetected using surveillance studies.

Comparison of the 2 oral regimens indicates that 1-mg weekly prophylaxis is more effective than 25-μg daily prophylaxis. The most likely explanation for this observation is the dosage; the cumulative dose per week was ~5 times higher in the weekly regimen (1.00 mg vs 0.18 mg for weekly and daily oral prophylaxis, respectively). It has been hypothesized that a high dosing frequency may require a relatively low dose of vitamin K to obtain good efficacy. However, our present data do not support the hypothesis that a daily dose of 25 μg is sufficient.

This study firmly establishes the efficacy of formula feeding in preventing VKDB in infants with unrecognized cholestasis. Formula feeding is even more effective than IM prophylaxis, the “gold standard,” to prevent VKDB. The mechanism underlying the preventive efficacy of formula feeding remains unclear. The vitamin K content of formula offers an insufficient explanation, because the average estimated daily intake of vitamin K in formula in our cohort (based on a daily formula intake of 150 mL/kg) is 25 to 50 μg, similar to the dose prescribed in the Dutch prophylactic regimen. A higher production of vitamin K by colonic bacteria in formula-fed infants might play a role. However, even a mixed-micellar vitamin K formulation, containing bile acids, is poorly absorbed in infants with biliary atresia.

Logistic regression revealed that female gender was a risk factor for VKDB. Although both genders were at a similar risk to present with a (severe) biochemical VKD, female infants were at a significantly higher risk of developing a VKDB. This result has not been reported previously, and the meaning of this finding is presently unknown.

CONCLUSIONS
We quantified the efficacy of frequent oral vitamin K prophylactic regimens in a cohort of Dutch and Danish biliary atresia infants. Our data clearly indicate that the current Dutch prophylaxis of 25 μg of daily oral vitamin K is insufficient to protect exclusively breastfed infants with biliary atresia from VKDB. Effective oral prophylaxis is feasible, as shown by the efficacy of a weekly oral dose of 1 mg of vitamin K in protecting these infants. Based on these data, the current Dutch prophylactic regimen is presently being reevaluated. We feel that nationwide prophylaxis should be tailored to protect those individuals who are at the highest risk to develop an adverse event. An event analysis in high-risk populations, as a means of “postmarketing” surveillance, could help to achieve this objective.

ACKNOWLEDGMENTS
We thank the Netherlands Study Group for Biliary Atresia Registry, which includes the following individuals: D. C. Aronson, A. Kindermann, C. M. F. Kneepkens, L. W. E. van Heurn, A. M. van den Neucker, Z. J. de Langen, P. M. J. G. Peeters, G. Madern, J. H. Escher, D. C. van der Zee, P. N. M. A. Rieu, and J. J. M. Tolboom.

REFERENCES
19. Forsgren L. Studies on the intestinal absorption of labelled


Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries
Peter M. van Hasselt, Tom J. de Koning, Nina Kvist, Elsemiek de Vries, Christina Rydahl Lundin, Ruud Berger, Jan L. L. Kimpen, Roderick H. J. Houwen, Marianne Horby Jorgensen and Henkjan J. Verkade
Pediatrics 2008;121:e857
DOI: 10.1542/peds.2007-1788

Updated Information & Services
including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/121/4/e857.full.html

References
This article cites 29 articles, 11 of which can be accessed free at: http://pediatrics.aappublications.org/content/121/4/e857.full.html#ref-list-1

Citations
This article has been cited by 3 HighWire-hosted articles: http://pediatrics.aappublications.org/content/121/4/e857.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Nutrition & Metabolism http://pediatrics.aappublications.org/cgi/collection/nutrition_and_metabolism

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml