TITLE: Neonatal Vitamin K Administration for the Prevention of Hemorrhagic Disease: A Review of the Clinical Effectiveness, Comparative Effectiveness, and Guidelines

DATE: 28 May 2015

CONTEXT AND POLICY ISSUES

Vitamin K deficiency in newborns may cause unexpected bleeding, historically referred to as hemorrhagic disease of the newborn (HDN) and now called vitamin K deficiency bleeding (VKDB). VKDB could occur between 0 and 24 hours (early), between two and seven days (classic), or between eight days to 12 weeks and up to six months (late) after birth.1,2 Late VKDB occurs mainly in infants who are fully breastfed and have received no or inadequate vitamin K prophylaxis at birth.1 The Canadian Paediatric Surveillance Program (CPSP) estimated the incidence of VKDB in Canada to be approximately 0.45 per 10^5 infants.3 This number included infants who received oral vitamin K or those who did not. Canada had the lowest incidence rate of VKDB compared to other countries such as Australia, Britain, Germany, New Zealand and Switzerland from 1995 to 2000.2

In 1961, the American Academy of Paediatrics (AAP) recommended intramuscular vitamin K to all newborns shortly after birth to prevent VKDB.4 However, there were studies suggesting a link between intramuscular vitamin K and an increased incidence of childhood cancer.4 Subsequent studies have been conducted and the Vitamin K Ad Hoc Task Force of the AAP reviewed the evidence and found no association between intramuscular administration of vitamin K and childhood leukemia and other cancers.4

For parents who decline intramuscular vitamin K, oral administration of vitamin K has been used as routine practice in some countries.5 A single dose of oral vitamin K may decrease the rates of early and classic VKDB, but not late VKDB.6 Multiple oral doses are needed for adequate protection against late VKDB, especially in fully breastfed infants.6 However, the oral vitamin K dosing regimen varies among countries.6

The aim of this report is to review the clinical effectiveness of intramuscular vitamin K, the comparative effectiveness between oral and intramuscular vitamin K, and guidelines regarding the administration of oral vitamin K for the prevention of VKDB.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness of intramuscular vitamin K administration to prevent hemorrhagic disease in neonates?

2. What is the comparative effectiveness of oral vitamin K versus intramuscular vitamin K to prevent hemorrhagic disease in neonates?

3. What are the evidence-based guidelines regarding administration of oral vitamin K for the prevention of hemorrhagic disease in neonates?

KEY FINDINGS

A single intramuscular dose of vitamin K prophylaxis could be sufficient to prevent VKDB in babies. Multiple oral doses of vitamin K according to the manufacturer instruction were recommended to be reserved for infants whose parents refused intramuscular administration. No data could be identified to compare the clinical effectiveness between oral and intramuscular vitamin K.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including, PubMed, The Cochrane Library, ECRI databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied. Where possible, retrieval was limited to the human population. The search was also limited to documents published between January 1, 2010 and April 27, 2015.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Population</th>
<th>Neonates</th>
</tr>
</thead>
</table>
| Intervention | Q1, Q2: Intramuscular vitamin K  
Q3: Oral vitamin K |
| Comparator | Q1, Q3: Any comparator, no comparator;  
Q2: Oral vitamin K |
| Outcomes | Q1: Clinical effectiveness (benefits, reduced hemorrhagic disease, safety, adverse events);  
Q2: Comparative effectiveness;  
Q3: Guidelines (including effective doses of oral vitamin K) |
| Study Designs | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines |
Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2010, duplicate publications of the same study, or included in a selected health technology assessment or systematic review.

Critical Appraisal of Individual Studies

The quality of systematic reviews was assessed using AMSTAR. The survey studies were critically appraised using the checklist designed by the Center for Evidence-based Management. The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument was used to evaluate the quality of the included guideline. For the critical appraisal of studies, a numeric score was not calculated. Instead, the strength and limitations of the studies were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 180 citations. Upon screening titles and abstracts, four potential relevant articles were retrieved for full-text review. Seven additional relevant reports were retrieved from other sources. Of the 11 potentially relevant articles, four reports were included in this review including one systematic review, two observational studies (retrospective cohort [survey]), and one guideline. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics of the systematic review and the observational studies are summarized in Appendix 2. Appendix 3 presents the grading of recommendations and levels of evidence of the included guidelines.

The systematic review by Martin-Lopez et al. (2011) aimed to determine the effectiveness of oral vitamin K compared to the intramuscular administration of vitamin K for the prevention of VKDB in newborns. A comprehensive literature search was conducted to identify all studies on using vitamin K to prevent VKDB with no language or date restriction, with searches until 30 April 2008. The primary outcome was spontaneous bleeding or bleeding following a circumcision. Other outcomes included biochemical parameters related to bleeding. Two RCTs comparing vitamin K administration to placebo or no treatment were identified. The quality of the studies was assessed using a validated assessment tool. No meta-analysis was employed in this systematic review.

The Swiss survey study by Laubscher et al. (2013) assessed data collected over a six-year period from July 1, 2005 to June 30, 2011. This period followed the acceptance of the new Swiss guidelines in 2003 to include a third dose of oral vitamin K (at week 4). The aim of this study was to determine whether the three doses of oral vitamin K could prevent VKDB in neonates as compared with the historical control cohort during the period where only two oral doses of vitamin K had been recommended. Survey questionnaires were sent to 728 pediatricians and the response rate was 86%. Data were analyzed from 458,184 live born infants in the 6-year study period.
The New Zealand survey study by Darlow et al 2011\textsuperscript{12} assessed data collected over an 11-year period from January 1998 to December 2008. The aim of this study was to determine the link between the receipt of vitamin K (intramuscular, oral or none) and VKDB in neonates. Questionnaires were sent to all registered paediatricians, paediatric surgeons, and clinicians working predominantly with children. The response rate was 94.5%. The total number of surveillance cards sent out and the number of live born infants were not reported.

The NICE guideline on postnatal care was originally published in July 2006,\textsuperscript{17} updated in December 2014, and last modified in February 2015. The guideline provides recommendations for care of mother and her baby during the postnatal period based on the best available evidence. Recommendations on the administration of vitamin K are part of those for maintaining infant health. The methodology of guideline development and evaluation of the science were described. Recommendations were graded according to the strength of the recommendation and quality of the supporting evidence (Appendix 3). There were no Canadian evidence-based guidelines identified.

**Summary of Critical Appraisal**

The strengths and limitations of the systematic review\textsuperscript{10} and the observational studies\textsuperscript{11,12} are summarized in Appendix 4. Those of the NICE guideline\textsuperscript{13,17} are presented in Appendix 5. The methodological quality of the systematic review\textsuperscript{10} was acceptable, as items such as a comprehensive literature search, lack of exclusion based on status of publication (i.e., grey literature searching), quality assessment of included studies, and conflict of interest statement met the AMSTAR checklist. However, some items were either not conducted or not reported including a priori design, duplication of study selection and data extraction, list of excluded studies, characteristics of included studies, use of scientific quality of the included studies in formulating the conclusions, and assessment of publication bias.

The quality of two observational studies,\textsuperscript{11,12} which were of survey type, was similar and appropriate with respect to research method, selection of population, rate of response, reporting and potential applicability to the Canadian newborn population. However, one study did not account for the potential confounding factor such as hepatobiliary disease, one of the main risk factors for VKDB.\textsuperscript{12} It was also unclear how the sample size was determined in both studies. The NICE guideline\textsuperscript{13,17} met all the items of the six main components of the AGREE II instrument. These include scope and purpose, stakeholder involvement, rigour of development, applicability, clarity of recommendation, and editorial independence. The guideline used systematic methods to search for the evidence, and clearly described the criteria for selecting the evidence, the strengths and limitations of the body of evidence, and methods of formulating the recommendations. In addition, the health benefits, side effects and risks were discussed and considered in formulating the recommendations.

**Summary of Findings**

**A. Clinical studies**

The main findings and authors’ conclusions of the systematic review\textsuperscript{10} and the observational studies\textsuperscript{11,12} are presented in Appendix 6.

The systematic review by Martin-Lopez et al. 2011\textsuperscript{10} included five reports including one Cochrane systematic review published in 2000 and four clinical trials which only measured biochemical parameters. From the Cochrane systematic review, two studies were found to have
bleeding outcomes from the comparison between intramuscular vitamin K and placebo or no treatment. One study published in 1960 showed that intramuscular vitamin K administration statistically significantly reduced bleeding after circumcision (relative risk \( RR \) 0.18 95% confidence interval [CI] 0.08 to 0.42). The other study published in 1967 found that intramuscular vitamin K administration statistically significantly reduced VKDB (RR [95% CI] 0.73 [0.56 to 0.96]). There were no studies that evaluated the clinical aspects of oral vitamin K versus placebo or no treatment, or oral versus intramuscular vitamin K. It was concluded that a single intramuscular dose of vitamin K is effective to prevent the classic form of VKDB.

In the Swiss survey study by Laubscher et al. 2013,¹¹ there were five confirmed VKDB cases found among 458,184 live born infants during the period of 2005 to 2011, in which three oral doses of vitamin K were recommended. Of the five cases, one case was of early VKDB and four cases were late VKDB. All five infants were fully breastfed. The estimated overall incidence of VKDB was 1.09 per \( 10^5 \) (95% CI 0.4 to 2.6). The incidence of late VKDB was 0.87 per \( 10^5 \) (95% CI 0.2 to 2.2). Of the four cases of late VKDB, there were three cases in which parents refused vitamin K prophylaxis, and one case in which the third dose had been forgotten. Parents also refused vitamin K prophylaxis in the case of early VKDB. Compared with the 1995-2001 data in which only two doses of oral vitamin K were given (18 cases of VKDB were detected among 475,372 live births), the overall incidence of late VKDB was statistically significantly lower with three oral doses (\( P = 0.007 \)). It was concluded that the oral administration of 3 x 2 mg mixed micellar vitamin K at hour 4, day 4, and week 4 after birth is effective to prevent VKDB.

In the New Zealand survey study by Darlow et al 2011,¹² 23 valid VKDB cases were detected between 1998 and 2008. Of those cases, there were three early, 10 classic, and 10 late VKDB. The three early VKDB were classified as ‘possible’. Of the 10 classic VKDB cases, eight were confirmed cases, of which none had received vitamin K prophylaxis and seven were fully breastfed. The incidence of classic VKDB was estimated to be 1.24 per \( 10^5 \) (95% CI 0.54 to 2.45). Of the 10 late VKDB cases, nine were confirmed cases, of which eight had received no vitamin K and were fully breastfed. The incidence of late VKDB was 1.40 per \( 10^5 \) (95% CI 0.64 to 2.65). It was concluded that, in New Zealand, fully breastfed infants who had not received vitamin K prophylaxis had a risk of VKBD.

**B. Guidelines**

The 2015 NICE Guideline¹³,¹⁷ had recommendations on the administration of vitamin K to newborns in maintaining infant health (Appendix 7). The recommendation statements were written in postnatal care guideline published in 2006¹⁷ and re-appeared in the updated version 2015.¹³ Briefly, it was recommended that vitamin K should be given intramuscularly as a single dose of 1 mg to all newborns to prevent VKDB [A]. If intramuscular vitamin K was declined by parents, it was recommended that multiple oral vitamin K doses should be offered according to the manufacturer instruction [D(GPP)]. The recommendations were made based on the high quality evidence that intramuscular route of vitamin K administration is more clinically effective and more cost effective than oral administration [Level 1+], there is no link between childhood cancer and intramuscular vitamin K prophylaxis [Level 1+], and multiple doses of oral vitamin K are required for adequate protection against late VKDB in breastfed babies [Level 1+].

**Limitations**

The systematic review¹⁰ might have some limitations, including potential publication bias, given that some studies may not have been published. During the literature search period, few studies on vitamin K prophylaxis were published or updated with bleeding outcomes. The evidence on
vitamin K prophylaxis in the prevention of VKDB was derived from two old studies published in 1960 and 1967. Also, there were no studies comparing oral versus intramuscular vitamin K that had bleeding outcomes found in the systematic review.

The apparent limitation of the two survey studies was that some cases might have not been reported despite high surveillance response rate. Severe bleeding cases were more likely to be reported, while mild-to-moderate cases that could be easily corrected by additional oral vitamin K would not be reported.

The NICE Guideline 2015\textsuperscript{13,17} had no apparent major limitations. There are no Canadian evidence-based guidelines could be identified in this literature search period.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

One systematic review, two survey studies and one guideline were retrieved. Results from the systematic review suggest that a single intramuscular dose of vitamin K is effective to prevent the classic form of VKDB in neonates. In one survey study, administration of three oral doses of vitamin K was better than two doses in the prevention of VKDB. In another survey study, fully breastfed infants not given vitamin K at birth were at risk of developing VKDB. Evidence for the comparative effectiveness of oral vitamin K versus intramuscular vitamin K in the prevention of VKDB, and evidence on safety of intramuscular vitamin K could not be identified. The guideline recommended a single intramuscular dose of vitamin K for all newborns as first option, and multiple doses of oral vitamin K as second option.

Although no Canadian evidence-based guidelines could be identified in the literature search, a Joint Position Statement from the Canadian Paediatric Society (CPS) and the College of Family Physicians of Canada (CFPC)\textsuperscript{14} was identified through the grey literature search. For the interest of this review in searching of recommendations with the Canadian context, it is noteworthy to mention here the recommendations from this Joint Position Statement. The statement for routine administration of vitamin K was published in 1997 and re-affirmed in 2014. It was recommended that a single intramuscular dose of vitamin K (0.5 mg for birthweight ≤1500 g or 1.0 mg for birthweight ≥1500 g) should be administered to all newborns within the first 6 hours after birth. If intramuscular vitamin K is refused by parents, an oral dose of 2 mg vitamin K was recommended at the time of first feeding, followed by a second dose at 2 to 4 weeks, and a third dose at 6 to 8 weeks. Also through the grey literature search, two practice guidelines, one from Perinatal Services British Columbia\textsuperscript{15} and one from the Winnipeg Regional Health Authority,\textsuperscript{18} were found and had similar recommendations regarding the administration of vitamin K for the prevention of VKDB in newborns.

Taken together, current evidence suggests that a single intramuscular dose or multiple oral doses of vitamin K prophylaxis could be sufficient to prevent VKDB in babies.
REFERENCES


APPENDIX 1: Selection of Included Studies

180 citations identified from electronic literature search and screened

176 citations excluded

4 potentially relevant articles retrieved for scrutiny (full text, if available)

7 potentially relevant reports retrieved from other sources (grey literature, hand search)

11 potentially relevant reports

7 reports excluded:
- 1 narrative review
- 6 non-evidence-based guidelines

4 reports included in review (1 systematic review, 2 observational studies, and 1 guideline)
APPENDIX 2: Characteristics of Included Clinical Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design, Length of Follow-up</th>
<th>Patient characteristics, sample Size (n)</th>
<th>Interventions</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Lopez et al. 2011 Spain</td>
<td>Systematic review</td>
<td>Two RCTs (1960, 1967) on IM vitamin K versus placebo or no treatment. The studies were found from the Cochrane systematic review 2000</td>
<td>Study 1960 (N=470 male infants): 5 mg IM vitamin K3 or nothing Study 1967 (N=3,338 full term infants): 100 mcg IM vitamin K3 (n=1,132), 5 mg IM vitamin K3 (n=1,063), or placebo (n=1,143)</td>
<td>• Clinical bleeding</td>
</tr>
<tr>
<td>Laubscher et al. 2013 Switzerland</td>
<td>Retrospective cohort study (survey)</td>
<td>Total live births: 458,184 Period: 2005 to 2011</td>
<td>Vitamin K prophylaxis (three oral mixed micellar phyloquinone)</td>
<td>• Clinical bleeding</td>
</tr>
<tr>
<td>Darlow et al. 2011 New Zealand</td>
<td>Retrospective cohort study (survey)</td>
<td>Total live births: not reported Period: 1998 to 2008</td>
<td>Vitamin K prophylaxis (IM, oral or none)</td>
<td>• Clinical bleeding</td>
</tr>
</tbody>
</table>

IM = intramuscular; RCT = randomized controlled trial
### APPENDIX 3: Grading of Recommendations and Levels of Evidence

<table>
<thead>
<tr>
<th>Guideline Society or Institute</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>NICE Guideline 2015UK</td>
<td>Grade A</td>
<td>1**: High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
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<tr>
<td></td>
<td>• At least one meta-analysis, systematic review, or randomized controlled trial (RCT) that is rated as 1**, and is directly applicable to the target population, or</td>
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<tr>
<td></td>
<td>• A systematic review or RCTs or a body of evidence that consists principally of studies rated as 1+, is directly applicable to the target population and demonstrates overall consistency of results, or</td>
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<td></td>
<td>• Evidence drawn from a NICE technology appraisal</td>
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<tr>
<td></td>
<td>Grade B</td>
<td>1*: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
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<td>• A body of evidence that includes studies rated as 2**, is directly applicable to the target population and demonstrates overall consistency of results, or</td>
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<tr>
<td></td>
<td>• Extrapolated evidence from studies rated as 1++ or 1+</td>
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<tr>
<td></td>
<td>Grade C</td>
<td>1: Meta-analyses, systematic reviews of RCTs with a high risk of bias</td>
</tr>
<tr>
<td></td>
<td>• A body of evidence that includes studies rated as 2+, is directly applicable to the target population and demonstrates overall consistency results, or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Extrapolated evidence from studies rated as 2++</td>
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<td></td>
<td>Grade D</td>
<td>2**: Well-conducted case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
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<tr>
<td></td>
<td>• Evidence level 3 or 4, or</td>
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<td></td>
<td>• Extrapolated evidence from studies rated as 2+, or</td>
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<td></td>
<td>• Formal consensus</td>
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<td></td>
<td>Grade D(GPP)</td>
<td>2+: Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
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<td>• A good practice point D(GPP) is a recommendation for best practice based on the experience of the Guideline Development Group</td>
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<td></td>
<td>Grade IP</td>
<td>3: Non-analytical studies (for example, case reports, case series)</td>
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<td></td>
<td>• Recommendation from NICE International Procedures guidance</td>
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<tr>
<td></td>
<td>Grade IP</td>
<td>4: Expert opinion, formal consensus</td>
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</table>

BC = British Columbia; CPS = Canadian Paediatric Society; NICE = National Institute for Health and Care Excellence; NHMRC = National Health and Medical Research Council; NR = not reported; UK = United Kingdom
# APPENDIX 4: Summary of Study Strengths and Limitations

<table>
<thead>
<tr>
<th>Author, year, type of study, country, design</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Martin-Lopez et al. 2011<sup>10</sup> Spain Systematic review | • A comprehensive literature search was performed.  
• The status of publication (i.e., grey literature) was used as an inclusion criterion.  
• The scientific quality of the included studies was assessed and documented.  
• The conflict of interest was stated. | • It was unclear if an “a priori” designed was provided.  
• It was unclear if there was duplicate study selection and data extraction.  
• The list of excluded studies was not reported.  
• The characteristics of the included studies were not provided.  
• It was unclear if the scientific quality of the included studies used appropriately in formulating conclusions.  
• The list of excluded studies was not reported.  
• The characteristics of the included studies were not provided.  
• It was unclear if the scientific quality of the included studies used appropriately in formulating conclusions.  
• The conflict of interest was stated. |
| Laubsher et al. 2013<sup>11</sup> Switzerland Retrospective cohort study (survey) | • The study addressed a clearly focused question.  
• The research method (study design) is appropriate for answering the research question.  
• The way the sample was obtained could not introduce (selection) bias.  
• The sample of subjects was representative with regard to the population to which the findings will be referred.  
• A satisfactory response rate was achieved.  
• The measurements (questionnaires) are likely to be valid and reliable.  
• Confidence intervals are given for the main results.  
• The statistical significance was assessed.  
• The results can be applied to the Canadian newborn population. | • The method of selection of the subjects (employees, teams, divisions, organizations is not clearly described.  
• It was unclear if the sample size was based on pre-study considerations of statistical power.  
• There could be confounding factors that haven’t been accounted for. |
| Darlow et al. 2011<sup>12</sup> New Zealand Retrospective cohort study (survey) | • The study addressed a clearly focused question.  
• The research method (study design) is appropriate for answering the research question.  
• The method of selection of the subjects (employees, teams, divisions, organizations is clearly described.  
• The sample of subjects was representative with regard to the population to which the findings will be referred.  
• A satisfactory response rate was achieved.  
• The measurements (questionnaires) are likely to be valid and reliable.  
• Confidence intervals are given for the main results.  
• The results can be applied to the Canadian newborn population. | • It was unclear if the way the sample was obtained could introduce (selection) bias.  
• It was unclear if the sample size was based on pre-study considerations of statistical power.  
• The statistical significance was not assessed.  
• There could be confounding factors that haven’t been accounted for. |
APPENDIX 5: Summary of Study Strengths and Limitations – Guidelines

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| NICE Guideline 2015<sup>13,17</sup> UK | **Scope and purpose**  
- Objectives and target patients population were explicit  
- The health question covered by the guidelines is specifically described  
- The population to whom the guidelines is meant to apply is specifically described  

**Stakeholder involvement**  
- The guideline development group includes individuals from all relevant professional groups  
- The views and preferences of the target population have been sought  
- The target users of the guideline are clearly defined  

**Rigour of development**  
- Systematic methods were used to search for evidence  
- The criteria for selecting the evidence are clearly described  
- The strengths and limitations of the body of evidence are clearly described  
- The methods of formulating the recommendations are clearly described  
- The health benefits, side effects, and risks have been considered in formulating the recommendations  
- There is an explicit link between the recommendations and the supporting evidence  
- The guideline has been externally reviewed by experts prior to its publication  
- A procedure for updating the guideline is provided  

**Applicability**  
- The guidelines provides advice and/or tools on how the recommendations can be put into practice  
- The guideline describes facilitators and barriers to its application  
- The potential resource implications of applying the recommendations have been considered  
- The guideline presents monitoring and/or auditing criteria  

**Clarity of recommendation**  
- The recommendations are specific and unambiguous | No major limitations |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td></td>
<td>• The different options for management of the condition or health issue are clearly presented</td>
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<td></td>
<td>• Key recommendations are easily identified</td>
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<td></td>
<td><strong>Editorial independence</strong></td>
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<tr>
<td></td>
<td>• The views of the funding body have not influenced the content of the guideline</td>
<td></td>
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<tr>
<td></td>
<td>• Competing interests of guideline development group members have been recorded and addressed</td>
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</table>
# APPENDIX 6: Main Study Findings and Authors’ Conclusions – Clinical

<table>
<thead>
<tr>
<th>Author, year, type of study, country, design</th>
<th>Condition / Interventions</th>
<th>Results</th>
</tr>
</thead>
</table>
| Martin-Lopez et al. 2011<sup>10</sup> Spain Systematic review | IM vitamin K versus placebo or nothing | Study 1960 (outcome: bleeding after circumcision): RR (95% CI) = 0.18 (0.08 to 0.42)  
Study 1967 (outcome: HDN/VKDB) RR (95% CI) = 0.73 (0.56 to 0.96) |

**Authors’ conclusions:** *“There is sufficient evidence to support the effectiveness of a single intramuscular dose of vitamin K to prevent the classic form of HDN”*<sup>10</sup> p 148

| Laubscher et al. 2013<sup>11</sup> Switzerland Retrospective cohort study (survey) | Vitamin K prophylaxis (three oral mixed micellar phylloquinone) |  
|-----------------------------------------------|-----------------------------|---------|
| | Five cases (one case of early and four cases of late VKDB)  
Overall incidence of VKDB was 1.09/10^5 (95% CI 0.4 to 2.6)  
Late VKDB incidence was 0.87/10^5 (95% CI 0.24 to 2.24)  
In three of four cases, parents had refused vitamin K prophylaxis  
In one of four cases, the third dose of vitamin K had been forgotten  
In historical cohort (475,372 live births) where newborns had received only two doses of oral vitamin K, 18 cases of VKDB were detected |

**Authors’ conclusions:** *“VKDB prophylaxis with 3x2 mg oral doses of mixed micellar vitamin K seems to prevent adequately infants from VKDB”*<sup>11</sup> p 357

| Darlow et al. 2011<sup>12</sup> New Zealand Retrospective cohort study (survey) | Vitamin K prophylaxis (IM, oral or none) |  
|-----------------------------------------------|-----------------------------|---------|
| | 23 valid cases (3 early, 10 classic, 10 late-onset) of VKDB were detected between 1998 to 2008  
3 early VKDB were classified as ‘possible’  
Of 10 classic VKDB, there were 8 confirmed cases; incidence 1.24/10^5 (95% CI 0.54 to 2.45); none had received no vitamin K; seven were fully breastfed  
Of the 10 late-onset VKDB, there were nine confirmed cases; incidence 1.40/10^5 (95% CI 0.64 to 2.65); eight had received no vitamin K; eight were fully breastfed |

**Authors’ conclusions:** *“In New Zealand, VKDB is virtually confined to fully breastfed infants not given vitamin K at birth”*<sup>12</sup> p 460

CI = confidence interval; HDN = hemorrhagic disease of newborn; IM = intramuscular; RR = relative risk; VKDB = vitamin K deficiency bleeding
### APPENDIX 7: Summary of Guideline Recommendations

<table>
<thead>
<tr>
<th>Guideline Society, Country, Author, Year</th>
<th>Recommendations</th>
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<tr>
<td>NICE Guideline 2015&lt;sup&gt;13,17&lt;/sup&gt; UK</td>
<td><strong>Recommendations</strong></td>
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<td>• “All parents should be offered vitamin K prophylaxis for their babies to prevent the rare but serious and sometimes fatal disorder of vitamin K deficiency bleeding. [A]&lt;sup&gt;17&lt;/sup&gt; p.265</td>
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<td>• “Vitamin K should be administered as a single dose of 1 mg intramuscular as this is the most clinically and cost effective method of administration. [A]&lt;sup&gt;17&lt;/sup&gt; p.265</td>
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<td>• “If parents decline intramuscular vitamin K for their baby, oral vitamin K should be offered as second line option. Parents should be advised that oral vitamin K must be given according to the manufacturer instructions for the clinical efficacy and will require multiple doses. [D(GPP)]&lt;sup&gt;17&lt;/sup&gt; p.265</td>
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<td>Evidence Statements</td>
<td>• “In light of available evidence it does not appear that there is a link between childhood cancer and IM vitamin K prophylaxis. [Level 1+]”&lt;sup&gt;17&lt;/sup&gt; p.271</td>
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<td>• “A single IM dose of 1 mg vitamin K appears to be effective prophylaxis for both early and late VKDB. [Level 1+]”&lt;sup&gt;17&lt;/sup&gt; p.271</td>
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<td>• “If oral vitamin K is given, multiple doses are required for adequate protection of breastfed infants against late VKDB. [Level 1+]”&lt;sup&gt;17&lt;/sup&gt; p.271</td>
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<td>• “The exact dosage and timing of oral vitamin K administration after the delivery dose has not been determined. [Level 2+]”&lt;sup&gt;17&lt;/sup&gt; p.271</td>
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<td>• “The intramuscular route of vitamin K administration appears to be more clinically effective and more cost effective. [Level 1+]”&lt;sup&gt;17&lt;/sup&gt; p.271</td>
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</table>

**BC** = British Columbia; **CPS** = Canadian Paediatric Society; **HDNB** = hemorrhagic disease of newborn; **IM** = intramuscular; **NICE** = National Institute for Health and Case Excellence; **NHMRC** = National Health and Medical Research Council; **NR** = not reported; **UK** = United Kingdom