Vitamin K for infants

To the Minister of Health, Welfare and Sport
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Health Council of the Netherlands

contents

executive summary

All infants are given vitamin K after birth. A deficiency of this vitamin can lead to bleedings that can cause life-long disability, especially if they occur in the brain. The way in which infants are administered vitamin K varies by country. In the Netherlands, all infants receive vitamin K in oral form immediately after birth. This dose is sufficient for infants who are formula-fed since the vitamin K in this type of nutrition adequately protects them against late-onset bleedings. This is not the case for breast-fed infants; therefore, they receive subsequent doses of oral vitamin K. In 2011, these subsequent doses were increased since in the Netherlands compared with other countries more bleedings occurred mainly in breast-fed infants with impaired fat absorption. These infants are less able to absorb vitamin K and therefore have a greater risk of a deficiency that could lead to a bleeding. Therefore, they represent a risk group. Recent data show that increasing the dose did not result in a reduction in the number of bleedings in this risk group. Therefore, the Committee on Nutrition of the Health Council of the Netherlands provided another overview of the latest scientific developments on vitamin K and will subsequently come up with a new recommendation.

Research on the optimal regimen of vitamin K administration has some limitations. There are no studies that directly compare the effect of different routes of administration of vitamin K to prevent bleeding. Therefore, the Committee relied on surveillance data on the efficacy of various foreign regimens. They showed that a single intramuscular administration of vitamin K provides better protection than current Dutch policy, including infants in the risk group. There is also an existing oral regimen that generally appears to provide better protection than current Dutch policy: the regimen from Germany and Switzerland, among other countries. It is unclear, however, whether this regimen is also more effective in the risk group. Another disadvantage of oral administration is that compliance plays a key role and that, for example, diarrhoea may reduce the absorption of the vitamin.

Since the infants belonging to the risk group cannot be identified at birth, the Committee recommends adapting the policy for all breast-fed infants. It advises switching to single intramuscular administration of one milligram of vitamin K shortly after birth. An important consideration is that this form of administration is known to be effective in infants from the risk group.

In addition, the Committee recommends offering an oral alternative to parents who do not want to have their child injected. This should consist of three times two milligrams of vitamin K (at birth, after 4 to 6 days and 4 to 6 weeks) for breast-fed infants.

For infants who are formula-fed starting at birth, vitamin K administration can continue as it now is (one milligram orally shortly after birth).

The Committee expects that the recommended new regimen as compared with current administration policy could prevent two to five cases of late vitamin K bleedings per year. Health professionals involved in perinatal care can administer the vitamin K via both routes. The Committee recommends discussing the importance and potential of vitamin K administration during pregnancy. Finally, it believes that providing appropriate information to both parents and professionals is important.

01 introduction

On 29 June 2010, the Health Council advised the Minister of Health, Welfare and Sport on administration of vitamin K to term infants in order to prevent bleeding due to a vitamin K deficiency. Such bleeding may result in life-long disability, particularly in the case of cerebral bleeding. The Health Council recommended maintaining the starting dose of one milligram at birth for all (both breastfed and formula-fed) infants, and increasing the recommended daily dose for breastfed infants from 25 micrograms to 150 micrograms.[1] The motivation for this recommendation was the observation that bleeding was more common in breasted infants with fat malabsorption in the Netherlands compared with other countries. The minister integrated this Health Council recommendation[2], and it was followed in the new Dutch guideline on vitamin K administration published by the Dutch Paediatrics Society (NVK).[3] The minister asked the involved professionals, including the NVK, to monitor the efficacy of the new vitamin K regimen.

Recently, a study on the effects of the updated guideline was published.[4] The researchers concluded that the current vitamin K regimen still fails to provide sufficient protection for breastfed infants with fat malabsorption. Based on these results, the NVK requested reassessment of the vitamin K regimen. Considering this information, the Minister requested the Health Council to advise on the current state of knowledge about vitamin K administration for infants aged 0-3 months and on possible changes to the regimen.

1.1 Method

The Nutrition Committee examined the matter and consulted parties that put these guidelines into practice, such as paediatricians, midwives, youth health care experts and GPs, as requested by the Minister. Two paediatricians, Dr. P.M. van Hasselt and Professor H.J. Verkade participated in a Committee meeting because of their expertise in this domain. Additionally, Dr. M.J. Shearer of the St. Thomas' Hospital in London was consulted – an internationally acknowledged expert in the field of vitamin K. The advisory report was reviewed by the Standing Committee on Health Care and the Standing Committee on Public Health. The President of the Health Council presented the advisory report to the Minister.

1.2 Reading guide

Firstly, the Committee briefly explains the considerations that resulted in the formulation of the previous advisory report in 2010, the uncertainties involved, and which of these uncertainties remain today. Secondly, the Committee discusses the recently published study that resulted in the present request for advice, and determined the current state of knowledge about vitamin K administration. Finally, it formulates its recommendation.

02 the current Dutch guideline

The current Dutch guideline prescribes a starting dose of one mg of oral vitamin K shortly after birth for all (both breastfed and formula-fed) infants. This is an effective way to prevent vitamin K deficiency bleeding during the first 24 hours after birth (early bleeding) and the first week after birth (classic bleeding).[3] However, the risk of vitamin K deficiency bleeding persists after the first week (late bleeding), particularly in breastfed infants. Unlike classic bleeding, such late bleeding is relatively common in the brain, and may result in a high disease burden for the rest of the child's life, or even death.[5]

Breastfed infants in particular are at risk for developing a vitamin K deficiency because vitamin K concentrations in breast milk are naturally low.[5] Therefore, they receive a daily dose of 150 micrograms of this fat-soluble vitamin orally during feeding from 8 days until three months.[3] In contrast, vitamin K in formula provides sufficient protection against late bleeding.[6] Therefore, formula-fed infants do not require additional vitamin K after the initial dose.[3] The minimum amount of formula sufficient for protecting infants against vitamin K deficiency bleeding is unknown. The NVK guideline sets 500 ml as the lower limit.[3]

In 2011, the daily dose of vitamin K for breastfed infants was increased from 25 to 150 micrograms, as the old dose proved insufficiently effective for preventing late vitamin K deficiency bleeding, particularly in breastfed infants with fat malabsorption.[6] This group is unable to absorb vitamin K adequately, resulting in a greater risk of deficiency and thus bleeding; the Committee therefore considers them to be a risk group. Fat malabsorption is generally caused by cholestatic liver disease. This means that bile transportation to the intestines is impeded or absent. This condition is present in about 1 in 5,000 infants.[7] A limited number of these infants can be identified early based on skin jaundice, warning bleeding around the navel, nosebleeds or bloody stools, and/or paler stools and dark yellow urine. There are currently no other options for early diagnostic testing.[8,9] Under the old regimen of 25 micrograms per day, about five infants with such an underlying condition suffered a serious bleed per year.[10]

The recommendation to administer follow-up doses of 150 micrograms per day to breastfed infants was based on the effective oral supplementation regimen used in Denmark until the year 2000, where infants received one milligram of vitamin K per week.[1] From 2000 onwards, infants in Denmark have received an intramuscular dose, in part because the oral preparation (cremophor) was no longer available.[11,12] The dosage frequency was based on the Dutch regimen for vitamin K (and D) supplementation, with the expectation that this would improve therapeutic compliance. Furthermore, it would prevent peaks in vitamin K plasma concentration. No recommendation was made about the type of vitamin K preparation in 2010.[1] In practice, parents can purchase oil-based vitamin K from drugstores, and healthcare professionals also use Konakion MM or Phytomenadion oral solution, both of which are sold by pharmacies.

There were a number of uncertainties surrounding the choice of the

follow-up dose. The most important one was a lack of scientific evidence for the best method for preventing vitamin K deficiency bleeding. This may explain why vitamin K administration methods vary per country. There are differences in the administration route (oral or intramuscular) and the administration regimens in terms of frequency, dosage and preparation used. Data on possible beneficial or harmful effects of higher vitamin K doses and peak concentrations in blood on bone quality, vascular wall function or brain function in healthy infants were also lacking.[1]

03 Efficacy of vitamin K regimens

The Committee notes that changes in the Dutch vitamin K regimen in 2011 did result in a decrease in late vitamin K deficiency bleeding, but did not have the desired effect in the high-risk group. Research in the high-risk group in the Netherlands and Denmark showed better results for a single intramuscular dose. This has been confirmed by international research based on surveillance data, which showed that there is also an oral alternative available that appears to outperform the Dutch regimen.

3.1 Efficacy of the current Dutch and Danish regimens for breastfed infants with fat malabsorption

Witt et al. presented the outcomes of monitoring data for the current Dutch supplementation regimen for infants with fat malabsorption due to the cholestatic liver disease biliary atresia in mid-2016[a].[4] They compared figures for the current Dutch regimen (for the period 2011-2015) with data from the previous Dutch regimen (for the period 1991-2011) and the intramuscular vitamin K regimen currently employed in Denmark (for the period 2000-2014).

The research showed that under the previous Dutch regimen, 82 percent of breastfed infants with biliary atresia developed a late vitamin K deficiency bleeding (in 45 of 55 examined events). Under the current Dutch regimen, this percentage remains unchanged; despite vitamin K administration, late bleeding due to vitamin K deficiency occurred in 9 of the 11 examined breastfed infants.[4] Although the number of cases is low, the Committee feels the conclusion that the updated vitamin K regimen has failed to achieve the intended effect in breastfed infants with biliary atresia is justified. The intramuscular vitamin K regimen employed in Denmark since 2000 clearly performs better. Infants in Denmark receive one milligram of vitamin K via intramuscular injection shortly after birth[11], with one of the 25 examined breastfed infants with biliary atresia (four percent) developing a late bleeding.[4]

According to the Committee, it is difficult to explain why the updated Dutch regimen has not resulted in the desired effect in the high-risk group compared to the old Danish regimen it was based on. The difference in dosage timing may play a role; while infants in Denmark received vitamin

[a] This condition is present in about 1 in 20,000 infants.

K in a single dose per week, the choice was made to administer daily doses in the Netherlands. The type of preparation used may also play a part.

3.2 Efficacy of the current Dutch regimen for general infant population

The current Dutch vitamin K regimen has resulted in a decreased number of late vitamin K deficiency bleeding in the general infant population. Surveillance data from the Netherlands Paediatric Surveillance Unit (NSCK) show that the number of cases has halved: from 3.2 per 100,000 in 2005[10] to 1.8 per 100,000 in the period between 2014 and August 2016 (personal report by Dr P.M. van Hasselt based on recent unpublished data). The number of cerebral bleeding cases has also decreased, as shown by the analyses of Dutch Paediatric Intensive Care Evaluation (PICE): prior to introduction of the current regimen (2008 to February 2011) the number of cerebral bleeding cases due to vitamin K deficiency was 3.1 per 100,000 births; after its introduction (March 2011 to 2015) it decreased to 1.2 per 100,000 births (personal report by Dr P.M. van Hasselt based on recent unpublished data). Despite this decrease, the number of vitamin K deficiency bleeding cases in the Netherlands under the current vitamin K regimen remains higher than in other Western countries where different regimens and dosage forms are used (Annex A).

3.3 Efficacy of the current international regimens for general infant population

Although no existing international vitamin K regimen is effective in preventing all vitamin K deficiency bleeding cases in infants, surveillance studies in the general infant population confirm the positive results of a single intramuscular vitamin K dose administered shortly after birth (incidence of 0.24 to 1.40 per 100,000 births).[13-16] Additionally, these studies describe an existing oral dosage form that appears to provide better protection than the current Dutch regimen.[12] This approach is used in for example Germany and Switzerland, where three doses of two milligrams are administered (at birth, after four to six days and after four to six weeks) (incidence 0.97 to 0.92 per 100,000 births (Annex A)).[17,18] However, this oral regimen has not been studied in the high-risk group.

04 considerations surrounding intramuscular and oral administration

The Committee considers that a single intramuscular dose of vitamin K provides better protection for breastfed infants with fat malabsorption than the current Dutch regimen, and considers that an oral vitamin K regimen used in other countries may also be more effective.

4.1 Intramuscular administration

As described above, a single intramuscular dose provides good protection against vitamin K deficiency bleeding for both the high-risk group and the general population of infants.[4,13-16] However, there are also other important aspects to consider for this administration route, such as parental acceptance and the risk of side-effects. Parents may be critical about injecting a newborn, for example because injections are painful, and they might therefore refuse the administration of vitamin K. However, this does not appear to be a major issue abroad. Research in countries where intramuscular administration is offered shows that a large number of infants receive vitamin K via injection. Percentages vary between 93 percent in New Zealand, where most births are supervised by a midwife, to over 99 percent in Canada, where most births are supervised by a physician.[19-21] Many countries offer parents who do not want to have their child injected an oral vitamin K alternative alongside the intramuscular route. Data from England indicated that refusal of any form of vitamin K supplementation is less common if parents are offered a choice of how they would like to administer it.[13] Refusal of intramuscular administration was more common in New Zealand and Australia in mothers with a normal delivery at home or at a birth centre under supervision by a midwife.[20,21] Parental objections to intramuscular administration in the US were primarily based on concerns about synthetic components in the injection, high doses and potential side-effects.[22] The group refusing vitamin K in both intramuscular and oral forms also often did not have their child vaccinated.[19]

There are still unanswered questions about the potential beneficial or harmful effects of peak concentrations of vitamin K in the blood. However, vitamin K has been administered intramuscularly for decades in various Western countries, to millions of infants[12], without any indication that intramuscular administration of vitamin K results in complications. Side-effects are very rarely reported. In the package leaflet, the manufacturer describes that intramuscular administration can lead to injection site irritation, although this is unlikely due to the low injection volume (0.1 ml). In very rare cases, this reaction is more severe, with inflammation and tissue damage at the injection site.[23-25] Over the years there have been incidental case reports of side-effects. For example, in the 1990s, cases of intramuscular bleeding were reported in children with coagulation disorders.[24] In 2014, there was a single report of anaphylactic shock without permanent harm in an infant, following intramuscular administration of vitamin K.[26]

There have also been reports of intramuscular administration of vitamin K in infants increasing the risk of developing acute lymphoblastic leukaemia.[27,28] However, studies into this topic are of poor methodological quality due to retrospective data collection. Later studies concluded there is no convincing evidence for this association.[5,29,30] Furthermore, acute lymphoblastic leukaemia is not more common in countries where vitamin K is administered via intramuscular injection compared to countries where it is administered via the oral route.[31-34] Based on these three arguments,

the Committee concludes this association is unlikely. Finally, there are a number of case reports of vitamin K being confused with a medication intended for the mother. This mostly involves the administration of ephedrine after delivery, a substance that can be lethal to the infant. In order to minimise this risk, the vial with vitamin K must be distinct from the vial containing medicines for the mother.[35]

In the late 1990s, research into the side-effects of a micellar vitamin K preparation (a solution with lectin and biliary salts that can be administered both via injection and orally) was published and which was based on reported cases to the manufacturer worldwide. Seventeen cases of side-effects were described in adults, including three serious cases, in 66 million patients who received a dose of ten to twenty milligrams (it is unclear if this was an oral or injected dose). This amounts to 0.026 side-effects per 100,000 patients, and 0.0045 serious side-effects per 100,000 patients.[36]

4.2 Oral administration

The Committee considered efficacy, the risk of side-effects and therapeutic compliance in evaluating the oral administration route. The efficacy of the existing oral alternative to intramuscular administration has not been studied in the high-risk group. There are uncertainties about the efficacy of oral regimens in this group, as these children have difficulty absorbing vitamin K via the digestive tract. Surveillance studies in the general infant population indicate that this approach (which is used in for example Germany and Switzerland), in which three doses of two milligrams are administered (at birth, after four to six days and after four to six weeks), appears to be more effective than the current Dutch regimen (Annex A).[12] A micellar preparation is used. As described above, side-effects of micellar preparations in adults are extremely rare. No side-effects were reported following two oral doses of two milligrams in one study of the micellar preparation in one to two million infants and children.[36]

Research into the absorption of vitamin K in fat droplets and vitamin K in a micellar form (Konakion MM) in cases of fat malabsorption is limited. There is one animal study in which the micellar form of vitamin K appears to be absorbed slightly better by rat intestines with fat malabsorption than vitamin K dissolved in fat droplets, although the difference was not statistically significant.[37] The degree to which the micellar form is absorbed is generally lower in infants with fat malabsorption compared to healthy infants, with the degree of absorption varying widely among infants with fat malabsorption.[38]

There may be problems with the efficacy of the oral preparation if the infant vomits the dose or has a lot of diarrhoea.[5,12] There is also a risk of poor therapeutic compliance with oral administration. This is due to the need for multiple administrations of a vitamin K dose over a longer period of time.[5] The starting dose is often administered by a healthcare professional involved in the birth. In some countries, for example Denmark (under the old oral regimen), follow-up doses are given by the parents.[6] In

other countries, this is done by healthcare professionals, for example during the health check-ups of the infants. Administration of follow-up doses can also be a shared responsibility of both parents and healthcare professionals.[39]

05 recommendations

There is no single scientifically proven vitamin K regimen that can prevent all vitamin K deficiency bleeding cases in breastfed infants, and given the lack of direct comparison studies on optimal vitamin K regimens, the Committee bases its recommendation primarily on insights from studies in the high-risk group, supplemented by surveillance data at the population level and practical considerations.

As it is impossible to predict which breastfed infants belong to the high-risk group at birth, and bleeding (particularly cerebral bleeding) may result in permanent disability, the Committee recommends changing to a single intramuscular dose of one milligram of vitamin K for all breastfed infants shortly after birth. This administration form has proven to be effective in the high-risk group, and data from surveillance studies in the general infant population confirm this (Annex A).[4,12] An important practical consideration is that intramuscular administration circumvents the uncertainties surrounding optimal preparation selection and related absorption problems in breastfed infants with fat malabsorption.

Furthermore, a single dose is sufficient, so therapeutic compliance is not a relevant issue.

The Committee recommends offering an oral alternative to parents who do not want to have their child injected. As only the Dutch oral regimen – and none of the other existing oral regimens – have been studied in the high-risk group, the Committee bases this recommendation on surveillance studies in which the current oral regimen in for example Germany and Switzerland, appears to be more effective than the Dutch regimen. The Committee recommends administrating three doses of two milligrams of vitamin K: at birth, after four to six days and four to six weeks. For infants who switch from breastfeeding to (non-hydrolysed) formula within four to six weeks, the follow-up doses may be skipped from the moment at least 500 ml of formula is provided. Because absorption of vitamin K by the intestines requires bile[5], which is released when fatty foods enter the intestines, it is recommended that vitamin K is given during breastfeeding. The Committee recommends promoting compliance with this alternative by employing the healthcare professionals already involved with the care for the infant to administer the vitamin K doses (maternity nurses, midwives, paediatricians and child healthcare employees).

The Committee recommends the administration of one milligram orally shortly after birth for infants who are formula-fed from birth, as described in the current guidelines. Research has shown this provides sufficient protection for these children.[6,9]

Infants receiving hydrolysed formula (hypoallergenic nutrition) have a

higher risk of vitamin K deficiency than infants who receive normal formula.[40] Therefore, the Committee recommends the same regimen as for breastfed infants in this group: one milligram administered intramuscularly or three times two milligrams of vitamin K in a micellar form as an alternative. So, if the oral alternative is selected, the Committee recommends giving breastfed infants who switch to hydrolysed formula within four to six weeks all follow-up doses.

Presented schematically, the new recommendation is as follows:

Recommended regimen	
Breastfed infants + infants receiving hydrolysed formula	Formula-fed infants
Preferred: 1 mg intramuscularly shortly after birth *Alternative:* 2 mg orally shortly after birth + 2 mg orally after 4-6 days[a] + 2 mg orally after 4-6 weeks[a]	1 mg orally shortly after birth
Current regimen	
Breastfed infants	Formula-fed infants
1 mg orally shortly after birth + 150 µg daily from day 8 to 3 months	1 mg orally shortly after birth

[a] If an infant consumes at least 500 ml of formula, this dose may be skipped.

It is expected two to five late vitamin K deficiency bleeding cases per year may be prevented by switching to the recommended regimen (the Committee elaborates on the calculation of this estimate in a background document).

Recommendations

The Committee recommends discussing and documenting the chosen administration route with expectant parents, so that involved healthcare professionals can administer the vitamin K in the desired manner at birth.

Before implementing the recommended vitamin K regimen, the Committee believes that good education of pregnant women and healthcare professionals involved in the care for infants is important. When educating parents, attention should be given to the dangers of vitamin K deficiency for the infant, the symptoms of fat malabsorption, and the advantages and disadvantages of various administration routes.

On scientific grounds, there are indications that formula-fed infants treated with one milligram of vitamin K administered orally are adequately protected from vitamin K deficiency bleeding.[6,9] This dose deviates from the dose recommended in the advised alternative oral regimen for breastfed infants. This could lead to practical difficulties with implementation. Therefore, the minister may consider recommending a single oral dose of two milligrams for formula-fed infants.

There is a single publication suggesting subcutaneous administration of vitamin K.[5] The advantage of this form of administration is that it is less painful than intramuscular administration. However, it is unknown whether subcutaneous administration of vitamin K is as effective as intramuscular administration. Therefore, the Committee recommends research to be conducted into the subcutaneous administration of vitamin K as an alternative to intramuscular administration.

The Committee has not considered the potential consequences for costs and funding of vitamin K administration. It also recommends continuing to monitor the vitamin K regimen, for example using the existing NVK monitoring systems.

literature

1 Health Council of the Netherlands. Advisory letter Vitamin K supplementation in infants. The Hague: Health Council of the Netherlands, 2010; publication no. 2010/11E.

2 Ministerie van Volksgezondheid, Welzijn en Sport. *Advisering gebruik vitamine K voor pasgeboren borstgevoede baby's*. Den Haag 2011; VGP/VC 3035513.

3 Winter JP de, Joosten KFM, IJland MM, Verkade HJ, Offringa M, Dorrius D, et al. *Nieuwe Nederlandse richtlijn voor vitamine K-toediening aan voldragen pasgeborenen*. Ned Tijdschr Geneeskd 2011; 155: A936.

4 Witt M, Kvist N, Hørby Jørgensen M, Hulscher JBG, Verkade HJ. *Prophylactic dosing of vitamin K to prevent bleeding*. Pediatrics 2016; 137(5): e20154222.

5 Shearer MJ. *Vitamin K deficiency bleeding (VKDB) in early infancy*. Blood Rev 2009; 23(2): 49-59.

6 Hasselt PM van, de Koning TJ, Kvist N, de Vries E, Lundin CR, Berger R, et al. *Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries*. Pediatrics 2008; 121(4): e857-e63.

7 Kneepkens CMF, Manrique ML, George EK, Bouwman DE. *Neonatale Cholestase*. Praktische Kindergeneeskunde. Maag-, darm- en leverziekten bij kinderen: 204. Houten: 2003. https://books.google.nl/books?id=XSU9cx-EQ5sC&pg=PA204&lpg=PA204&dq=incidentie+cholestase+zuigelingen&source=bl&ots=oJE5IK1Peh&sig=qwNTqBmMoQTCfaSMyE8niR9sDOE&hl=nl&sa=X&ved=0ahUKEwin26uEq6PSAhVIIMAKHV-_AZMQ6AEIGjAA#v=onepage&q=incidentie%20cholestase%20zuigelingen&f=false. Consulted: 09/03/2017.

8 McNinch A, Tripp J. *Haemorrhagic disease of the newborn in the British Isles: two year prospective study*. BMJ 1991; 303: 1105-9.

9 Sutor AH, Von Kries R, Cornelissen EA, McNinch A, Andrew M. *Vitamin K deficiency bleeding (VKDB) in infancy*. Thromb Haemost 1999; 81: 456-61.

10 IJland MM, Pereira RR, Cornelissen EA. *Incidence of late vitamin K deficiency bleeding in newborns in the Netherlands in 2005: evaluation of the current guideline*. Eur J Pediatr 2008; 167(2): 165-9.

11 Krag E, Skak-Iversen L. Sundhedsstyrelsen. *Meddelese af 23. maj 2000 om ændrede retningslinier vedr. anvendelse af K-vitamin til nyfødte og spæde børn Til landets fødesteder, jordemødre, sundhedsplejersker og alment praktiserende læger*. Kopenhagen, 2000. http://sundhedsstyrelsen.dk/publ/Off_Medd/officiel_meddelelse_k_vitamin1.pdf. Consulted: 09/03/2017.

[12] Mihatsch W, Braegger C, Bronsky J, Compoy C, Domellöf M, Fewtrell M, et al. *Prevention of vitamin K deficiency bleeding in newborn infants: a position paper by the ESPGHAN committee on nutrition*. J Pediatr Gastroenterol Nutr 2016; 63(1): 123-9.

[13] Busfield A, Samuel R, McNinch A, Tripp JH. *Vitamin K deficiency bleeding after NICE guidance and withdrawal of Konakion Neonatal: British Paediatric Surveillance Unit study, 2006-2008*. Arch Dis Child 2013; 98(1): 41-7.

[14] McMillan DD, Grenier D, Medaglia A. *Canadian Paediatric Surveillance Program confirms low incidence of hemorrhagic disease of the newborn in Canada*. Paediatr Child Health 2004; 9(4): 235-8.

[15] Canadian Paediatric Surveillance Program. *Vitamin K injection - best prevention for newborns*. Paediatr Child Health 2002; 7(8): 588-9.

[16] Darlow BA, Phillips AA, Dickson NP. *New Zealand surveillance of neonatal vitamin K deficiency bleeding (VKDB): 1998-2008*. J Paediatr Child Health 2011; 47(7): 460-4.

[17] Von Kries R, Hachmeister A, Göbel U. *Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding*. Arch Dis Child Fetal Neonatal Ed 2003; 88(2): F109-12.

[18] Laubscher B, Bänziger O, Schubiger G, Swiss Paediatric Surveillance Unit. *Prevention of vitamin K deficiency bleeding with three oral mixed micellar phylloquinone doses: results of a 6-year (2005-2011) surveillance in Switzerland*. Eur J Pediatr 2013; 172(3): 357-60.

[19] Sahni V, Lai FY, MacDonald SE. *Neonatal vitamin K refusal and nonimmunization*. Pediatrics 2014; 134(3): 497-503.

[20] Khambalia AZ, Roberts CL, Bowen JR, Nassar N. *Maternal and infant characteristics by mode of vitamin K prophylaxis administration*. J Paediatr Child Health 2012; 48(8): 665-8.

[21] Burke M, Bernhardt H, Reith DM, Barker D, Broadbent RS, Wheeler BJ. *Perinatal influences on the uptake of newborn Vitamin K prophylaxis--a retrospective cohort study*. Aust N Z J Public Health 2015; 39(6): 573-6.

[22] Hamrick HJ, Gable EK, Freeman EH, Dunn LL, Zimmerman SP, Rusin MM, et al. *Reasons for Refusal of Newborn Vitamin K Prophylaxis: Implications for Management and Education*. Hospital Pediatrics 2016; 6(1): 15-21.

[23] Roche. *Bijsluiter: informatie voor de gebruiker. Konakion MM voor kinderen 2mg/0,2ml oplossing voor injectie en oraal gebruik.* Woerden, 2014. http://www.roche.nl/wp-content/uploads/2014/12/Konakion_paed_QRDv3_27nov14_B.pdf. Consulted: 09/03/2017.

[24] Sutor AH. *Vitamin K Deficiency Bleeding in Infants and Children*. Semin Thromb Hemost 1995; 21(03): 317-29.

[25] College ter Beoordeling van Geneesmiddelen. *Konakion MM voor kinderen 2mg/0,2ml oplossing voor injectie en oraal gebruik*. 2016. http://db.cbg-meb.nl/IB-teksten/h03809.pdf. Consulted: 09/03/2017.

[26] Koklu E, Taskale T, Koklu S, Ariguloglu EA. *Anaphylactic shock due to vitamin K in a newborn and review of literature*. The Journal of Maternal-Fetal & Neonatal Medicine 2014; 27(11): 1180-1.

[27] Golding J, Greenwood R, Birmingham K, Mott M. *Childhood cancer, intramuscular vitamin K, and pethidine given during labour*. BMJ 1992; 305: 341-6.

[28] Parker L, Cole M, Craft AW, Hey EN. *Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study*. BMJ 1998; 316(7126): 189-93.

[29] Fear NT, Roman E, Ansell P, Simpson J, Day N, Eden OB, et al. *Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study*. Br J Cancer 2003; 89(7): 1228-31.

[30] Roman E, Fear NT, Ansell P, Bull D, Draper G, McKinney P, et al. *Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies*. Br J Cancer 2002; 86(1): 63-9.

[31] Integraal Kankercentrum Nederland. *Cijfers over kanker: Incidentie lymfoblastaire leukemie/lymfoom*. http://www.cijfersoverkanker.nl/selecties/dataset_1/img58a423130089a. Consulted: 02/02/2017.

[32] Australian Institute of Health and Welfare. *Australian Cancer Incedence and Mortality books: Acute lymphoblastic leukaemia*. http://www.aihw.gov.au/acim-books/. Consulted: 03/02/2017.

[33] Association of Population-Based Cancer Registries and Robert Koch Institute. *Cancer in Germany*. 2016. http://www.krebsdaten.de/Krebs/EN/Content/Publications/Cancer_in_Germany/cancer_chapters_2011_2012/cancer_children.pdf;jsessionid=61D7A4E1798049EDEBFDB7D9467D17AB.2_cid363?_blob=publicationFile. Consulted: 03/02/2017.

[34] American Cancer Society. *Childhood and adolescent cancer incidence rates, 2009-2013*. https://cancerstatisticscenter.cancer.org/#/data-analysis/ChildIncRate. Consulted: 02/02/2017.

[35] Seidelin J, Pedersen BL, Mogensen TS. *Risk management by reporting critical incidents. Vitamin K and ephedrine mix-up at a birthing unit*. Ufeskr Laeger 2001; 163(39): 5365-7.

[36] Pereira SP, Williams R. *Adverse Events Associated with Vitamin K1: Results of a Worldwide Postmarketing Surveillance Programme*. Pharmacoepidemiology and Drug Safety 1998; 7(3): 173-82.

[37] Hasselt PM van, Minderhoud TC, Slot TK, van der Ham M, Janssens GEPJ, de Sain M, et al. *The influence of the gastric environment on the absorption of vitamin K from orally administered mixed micelles under physiological and bile deficient conditions*. Vitamin K prophylaxis revisited: Focus on risk factors (Thesis): 108-25. Utrecht: van Hasselt, P.M.; 2009.

[38] Pereira SP, Shearer MJ, Williams R, Mierli-Vergani G. *Intestinal absorption of mixed micellar phylloquinone (vitamin K1) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding*. Arch Dis Child Fetal Neonatal Ed 2003; 88(2): F113-8.

[39] Auckland District Health Board. *Vitamin K prophylaxis and vitamin K deficiency bleeding*. http://www.adhb.govt.nz/newborn/Guidelines/Blood/VitaminK.html. Consulted: 09/03/2017.

[40] Hasselt PM van, de Vries W, de Vries E, Kok K, Cranenburg EC, de

Koning TJ, et al. *Hydrolysed formula is a risk factor for vitamin K deficiency in infants with unrecognised cholestasis*. J Pediatr Gastroenterol Nutr 2010; 51(6): 773-6.

41 Statista Das Statistik-Portal. *Anzahl der Geburten in Deutschland von 1991 bis 2015*. https://de.statista.com/statistik/daten/studie/235/umfrage/anzahl-der-geburten-seit-1993/. Consulted: 02/02/2017.

annex

A Efficacy of international vitamin K regimens in the general infant population

The table shows the number of late vitamin K deficiency bleeding cases for various existing vitamin K regimens based on surveillance studies in the general infant population. As a proportion of infants does not receive vitamin K in practice, a distinction has been made between the total number of late vitamin K deficiency bleeding cases during the study period (regardless of vitamin K administration) and the number of late vitamin K deficiency bleeding cases where the infant did receive vitamin K. The number of late vitamin K deficiency bleeding cases is limited, although no existing regimen appears to be effective in preventing all late vitamin K deficiency bleeding. Without additional vitamin K, the incidence of vitamin K deficiency bleeding is between 4-7 cases per 100,000 births.[5]

Table 1. Number of late vitamin K deficiency bleeding events under two oral regimens and one intramuscular regimen (with an oral alternative) in the general population of infants

Country	Number of births	Incidence per 100,000 (95% confidence interval)	Number of late vitamin K deficiency bleeding cases			
			Total	With vitamin K (administration route)	Incomplete amount of vitamin K	Without vitamin K[a]
One milligram orally for all infants with follow-up doses of 150 micrograms for breastfed infants						
The Netherlands, 2014-2016	333,333[b]	1.8	6c	5	-	1
Three doses of two milligrams for all infants						
Germany[17] 1997-2000	3,138,695	0.92[d]	29[e]	17[c]	2	7
Switzerland[18] 2005-2011	458,184	0.87 (0.24-2.24)	4[c]	0	1	3
One milligram intramuscularly for all infants, with an oral alternative						
England[13] 2006-2008	1,700,000	0.24 (0.00-0.35)[f]	4[c]	1 (intramuscular)	1	2
Canada[14] 1997-2000	1,360,000	0.37	5[c]	3 (1 oral; 2 intramuscular)	-	2
Australia[15] 1995-2000	1,500,000[b]	0.60	9[g]	6 (3 oral; 3 intramuscular)	-	3
New Zealand[16] 1998-2008	642,857[b]	1.40 (0.64-2.65)	9[c]	1 (intramuscular)	-	8

[a] No vitamin K because parents refused vitamin K or it was not given by mistake.

[b] Estimate of the number of births based on the number of later bleeding cases and incidence figure.

[c] All cases breastfed, underlying liver diseases present in four out of six cases in the Netherlands, fourteen out of seventeen cases in Germany, four out of four cases in Switzerland, two out of four cases in England, one out of five cases in Canada (oral vitamin K) and six out of nine cases in New Zealand.

[d] Own calculation based on data from the article combined with the number of births in Germany during that period.[41] In the group of infants who received the micellar form of vitamin K, the incidence was 0.44 per 100,000.

[e] For three children, there is no data available on whether they received vitamin K.

[f] Two cases of late bleeding were not included in the incidence figure presented in the article because they occurred after three months (the international cut-off for late vitamin K deficiency bleeding); these were a formula-fed infant with underlying liver disease who had received 0.5 milligrams of vitamin K intramuscularly, and a formerly breastfed infant without liver disease who had received 0.3 mg of vitamin K intramuscularly.

[g] No information available on type of nutrition and underlying liver disease.

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