Prevention of Vitamin K Deficiency Bleeding in Newborns – A New Guidelines



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Aim

To present new guidelines for the prevention of vitamin K deficiency bleeding (VKDB) in newborns

Outline

- Physiological role of vitamin K
- About Vitamin K Deficiency Bleeding in newborns
- Causes of primary and secondary deficiency of vitamin K in newborns
- Wy prophylactic use of vitamin K is important?
- Strategies of prophylactic vitamin K use in different countries
- Cost effectiveness of vitamin K prophylaxis

Prevalence of coagulation disorders in neonates

- in **40%** newborns at autopsy
- In **1%** of newborns admitted to NICU

Clin Perinatol 1984;11:309-37

The most frequent acquired hemorrhagic disorders in neonates:

- DIC
- **vitamin K deficiency**
- liver disease

Semin Perinatol 1997;21:70-85

The role of vitamin K in human body

The coagulation

- vitamin K dependent coagulation factors **II, VII, IX, X**

- Vitamin K dependent anticoagulation factors proteins **C, S i Z**

J Lipid Res 2014;55(3):345-62.

The role of vitamin K in human body

- vitamin K **does not influence the primary gene product** while it acts in the **posttranslational process activating inactive PIVKA proteins**

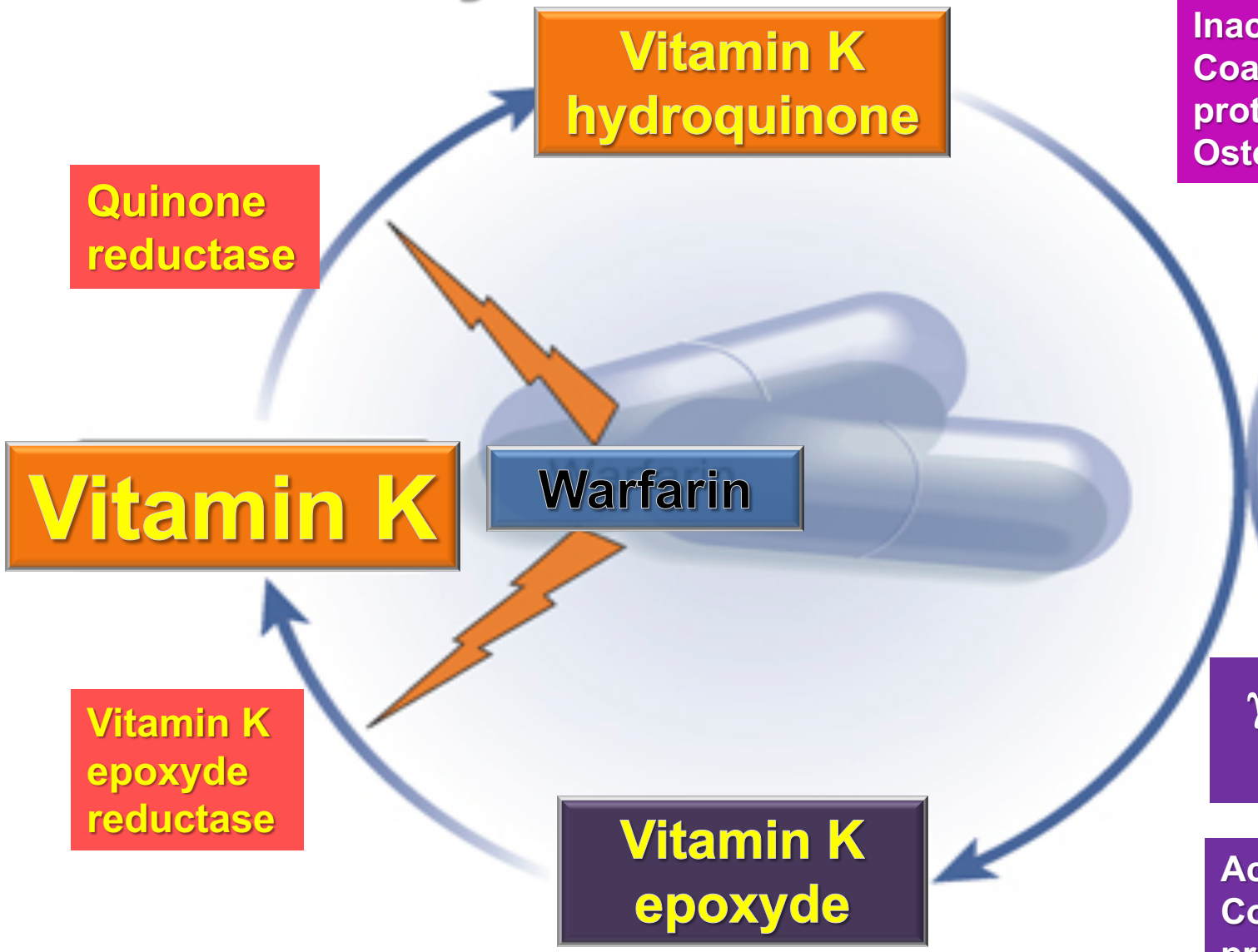
- The role of vitamin K in the ossification is not clearly understood

J Nutr Gerontol Geriatr 2014;33(1):10-22.

Am J Health Syst Pharm 2005;62:1574-81.

J Lipid Res 2014;55(3):345-62.

Vitamin K cycle



Inactive
Coagulation factors II, VII, IX, X,
proteins C, S, Z
Osteocalcin

Proteins

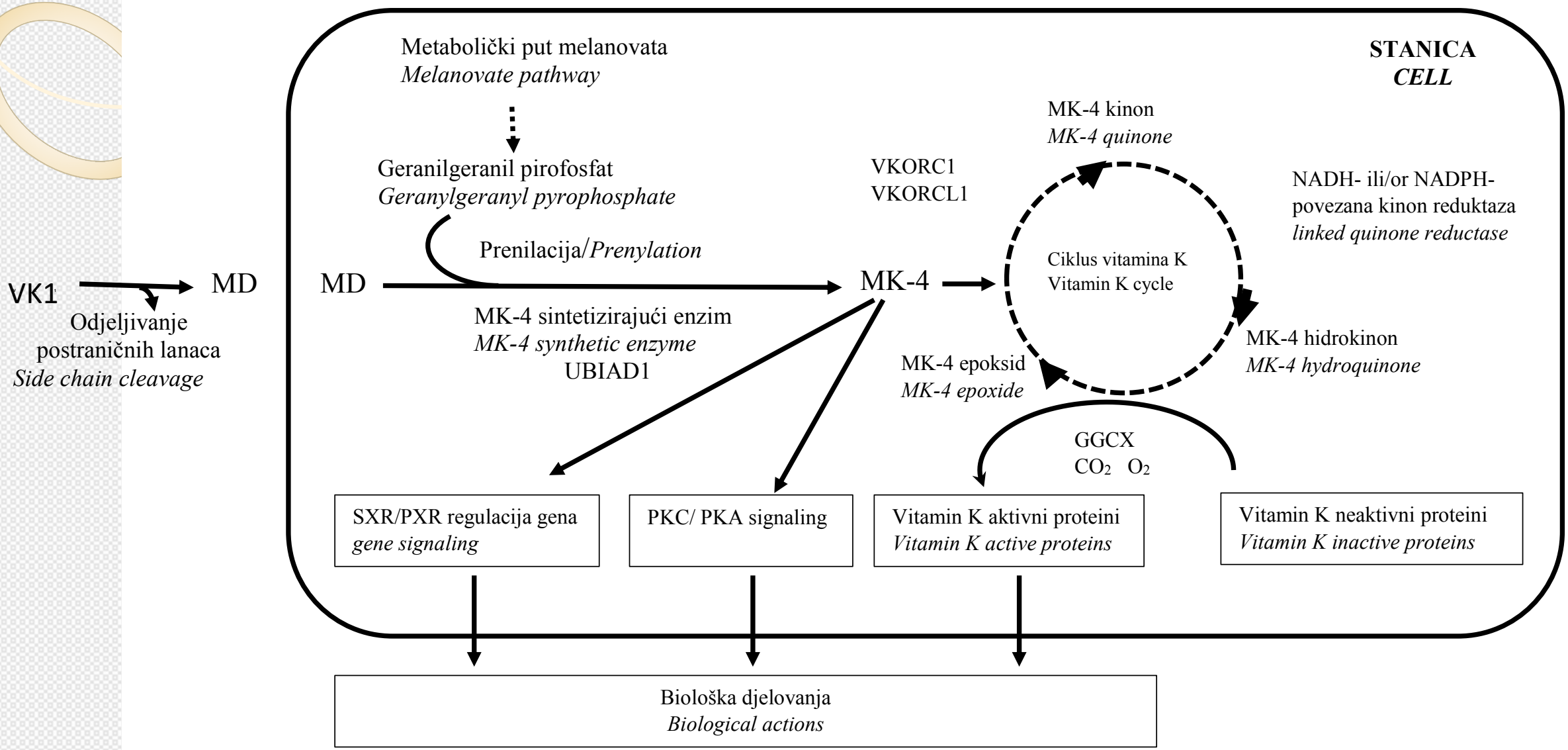
γ-glutamyl carboxylase

γ-carboxylated proteins

Active
Coagulation factors IIa, VIIa, IXa, Xa,
proteins Ca, Sa, Za
Osteocalcin a

J Thromb Haemost. 2013 Aug; 11(8): 1556–1564. doi: 10.1111/jth.12306

A new paradigm on vitamin K function



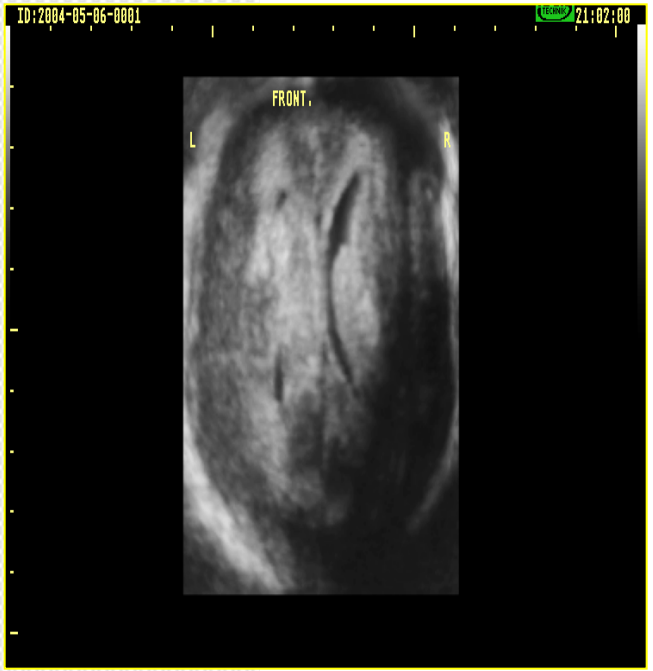
Okano T. A new horizon in vitamin K research. **Yakugaku Zasshi. 2016;136(8):1141-59**. doi: 10.1248/yakushi.16-00014.

Definition of vitamin K deficiency bleeding or hemorrhagic disease of newborns (VKDB/HDN)

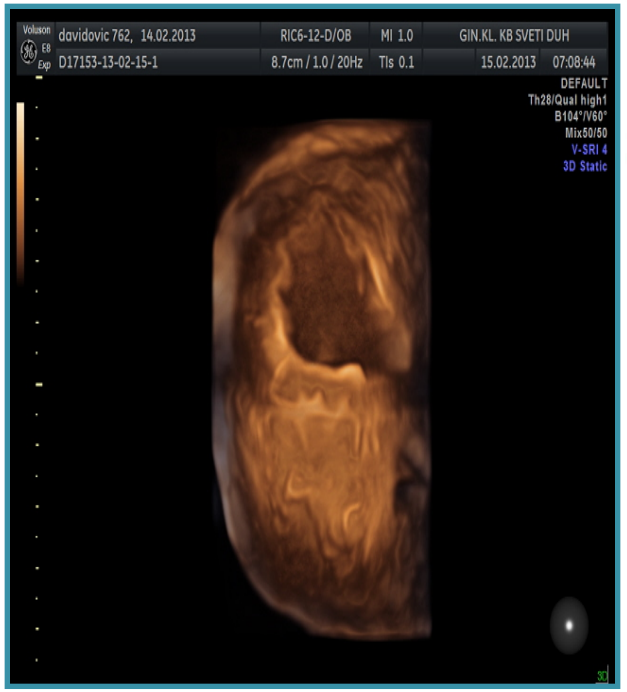
Bleeding appearing more often in **breastfed infants**, occurring predominantly in the early neonatal period but can be observed **during the entire infancy**, caused by primary or secondary **vitamin K deficiency** with coagulation disorders, which can be reverted by administration of vitamin K.

Stanojević M. Prevencija ranog, klasičnog i kasnog oblika hemoragijske bolesti u zdrave i donošene novorođenčadi (magistarski rad). Zagreb: Medicinski fakultet Sveučilišta u Zagrebu, 1991:116 str.

Classification of VKDB/HDN











Three forms of VKDB (HDN) in neonates

- **Early onset** (in the first 24 hour after birth)
- **Classic** (from the 2nd to 7th day of life)
- **Late-onset** (from 8th day of life, most common in the first 12 weeks, but can occur in the first 12 months of life)

Eur J Pediatr 2009;168(2):127-34. doi: 10.1007/s00431-008-0856-1.
Early Hum Dev 2010; 86 (Suppl 1): 63 - 5. doi: 10.1016/j.earlhumdev.2010.01.017.
MMWR Morb Mortal Wkly Rep 2013;62(45):901-2.

Causes of primary vitamin K deficiency in infants



Natural sources of vitamin K



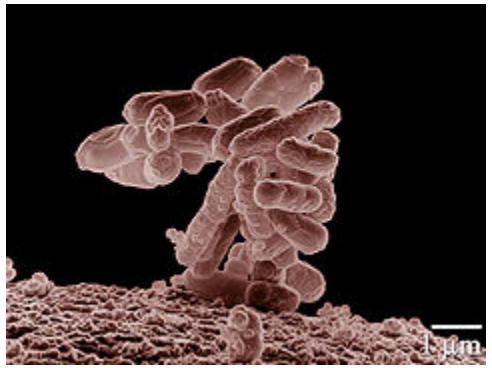


Green plants

vitamin K1- **phylloquinone, phytomenadione, or phytonadione**

Anaerobic bacteria of the intestinal flora

Vitamin K2 - **menaquinones**





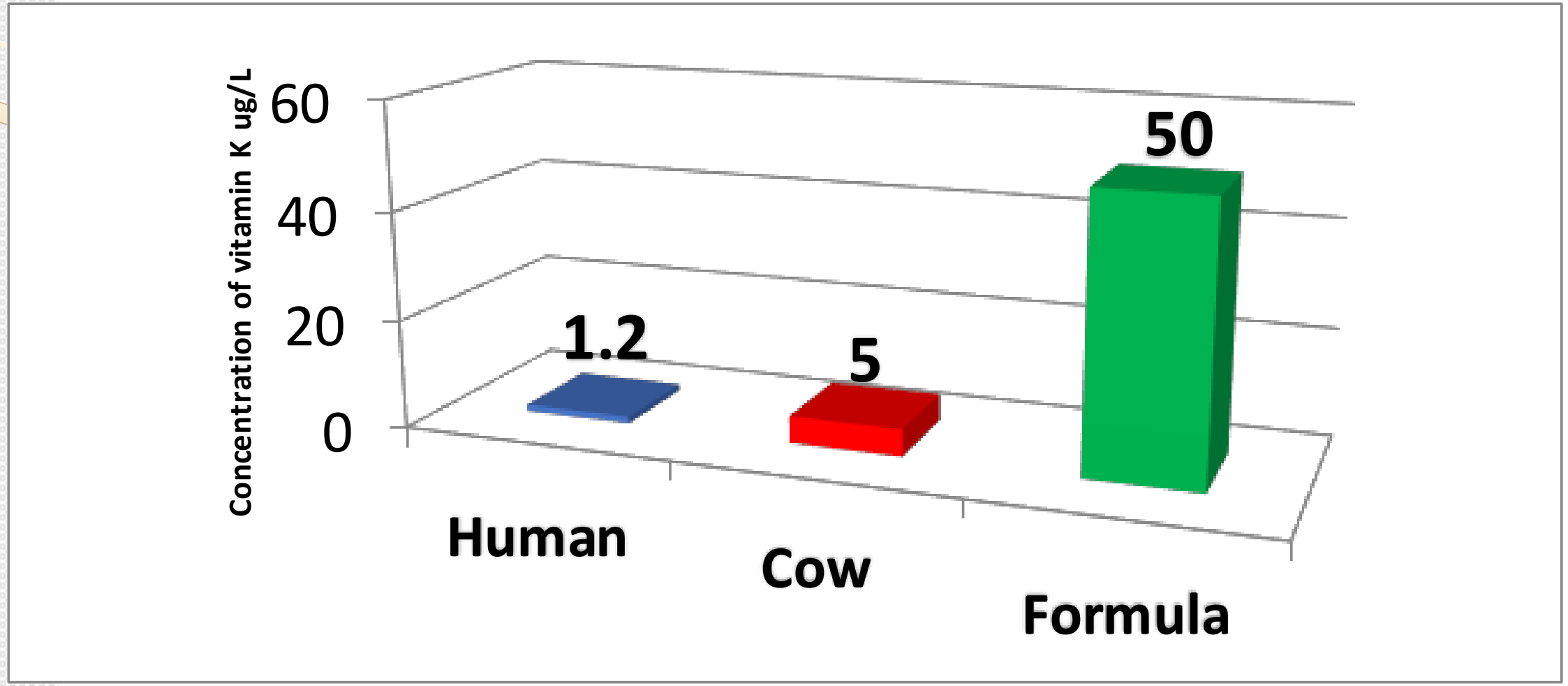
Primary vitamin K deficiency in infants

1. Poor transplacental transfer of vitamin in pregnancy
(concentration of vitamin K in fetal liver is only 5% to 25% of the mother's plasma concentration)

2. Low levels of vitamin K in the breast milk

MMWR Morb Mortal Wkly Rep 2013;62(45):901-2.

Low concentration of vitamin K in the breastmilk



MMWR Morb Mortal Wkly Rep 2013;62(45):901-2.

Phylloquinone content in human milk and infant formula

Nutrient	Phylloquinone content	
	mg/100 mL	mg/L
Human milk		
Term colostrum	0,23	2,3
Term expressed breast milk	0,21	2,1
Preterm colostrum	0,30	3,0
Infant formula		
PreAptamin	6,6	66
Aptamil	4.0	40
Nan 1	5,55	55,5
Pre Nan	6,44	64,4
Aptamil Pronutra +	6,1	61

Nutrients. 2015;7(10):8308-20. doi: 10.3390/nu7105393.

Primary vitamin K deficiency in infants

3. Decreased production of vitamin K by enteral bacterial flora of breastfed neonates

(until the age of 14 days the amount of bacteria of the intestinal flora of the newborn becomes the same as that in later infancy)

MMWR Morb Mortal Wkly Rep 2013;62(45):901-2.

Causes of secondary vitamin K deficiency in infancy



Secondary vitamin K deficiency in newborns – maternal causes

1. Pregnant women treated with warfarin, antiepileptic drugs, tuberculostatics and antibiotics more than 14 days

2. Pregnant women with vitamin K deficiency (vitamin K avitaminosis)

Early Hum Dev 2010; 86 (Suppl 1): 63 - 5. doi: 10.1016/j.earlhumdev.2010.01.01

Secondary vitamin K deficiency in newborns – neonatal causes

1. Delayed breastfeeding
2. Cholestasis, vitamin K malabsorption, prolonged jaundice, diarrhea lasting more than 7 days
3. **Liver diseases of various etiologies**
4. Antibiotic or warfarin treatment lasting more than 14 days

Early Hum Dev 2010; 86 (Suppl 1): 63 - 5. doi: 10.1016/j.earlhumdev.2010.01.01

Incidence of late vitamin K deficiency bleeding in developed and developing countries

Countries	Median incidence on 100.000 live births	Range
Middle and low income	35	10,5-80
High income	80	72-80
All countries	8,8	5,8-17,8

Sankar MJ, Chandrasekaran A, Kumar P, Thukral A, Agarwal R,Paul VK. Vitamin K prophylaxis for prevention of vitamin K deficiency bleeding: a systematic review. **J Perinatol. 2016; 36(Suppl 1): S29–S35.doi: 10.1038/jp.2016.30.**

Adequate Daily Intake of vitamin K in adults

- **R**ecommended **D**aily **A**llowance – **RDA** of vitamin K are not known

- Adequate Daily Intake of vitamin K in adults is
  - **90** (women) to
  - **120** (men) mg/day.

J Lipid Res 2014;55(3):345-62.

Br J Nut 2013;110(8):1357-68.

Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press (US), Washington (DC): 2001.

Adequate Daily Intake of vitamin K in infants

- Infants from **0 to 6 months** Adequate Daily Intake (ADI) is **2,0 mg/day**

- **7 to 12 months 2,5 mg/day**

Br J Nut 2013;110(8):1357-68.

Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press (US), Washington (DC): 2001.

Estimated daily intake of vitamin K in exclusively breastfed infants

Day of lactation	Concentration of phylloquinone in breast milk (mg/L)	Estimated daily intake of phylloquinone in exclusively breastfed infants mg/day
3 days	1,10	0,86
2 weeks	1,17	0,92
6 weeks	1,14	0,89
12 weeks	1,7	0,92

Adequate daily intake of vitamin K for infants from 0 t0 6 months is 2,0 μg/day

MMWR Morb Mortal Wkly Rep 2013;62(45):901-2.

Are there deposits of vitamin K in humans?

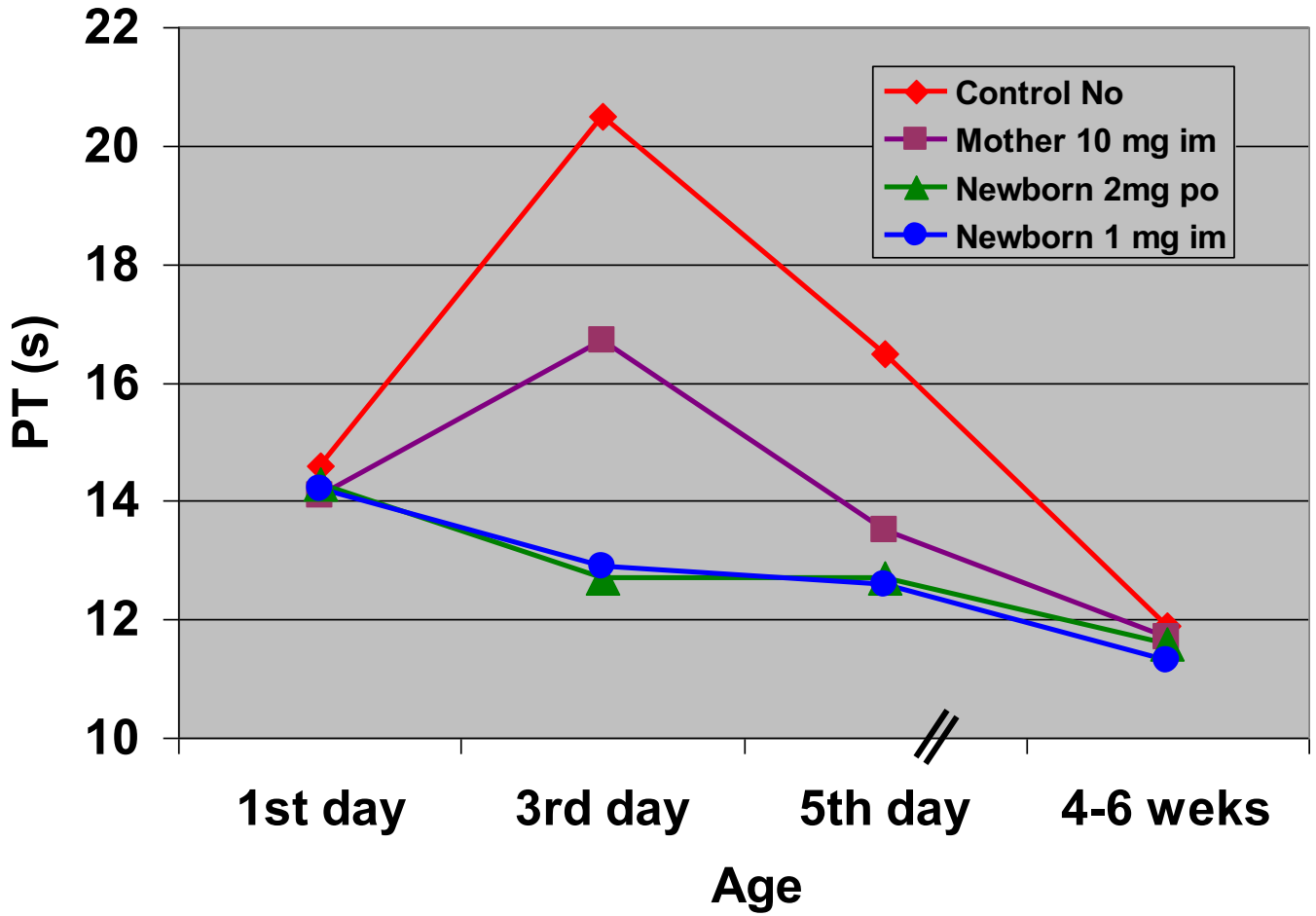
- There is **vitamin** K in the **liver**, but still it is not known where are depostis of vitamin K in human body
- It is well known that vitamin K can be found in the **brain, kidneys and pancreas**, but it still not known what is its' role in these organs

J Lipid Res 2014;55(3):345-62.

Br J Nut 2013;110(8):1357-68.

Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press (US), Washington (DC): 2001.

Influence of vitamin K_1 application to the mothers at least six hours before delivery on prothrombin time of infants in the first six weeks of life



CMJ 1996;37:84-8; Gynecol Perinatol 1994;3:39-43

The route of administration of vitamin K

- American Academy of Pediatrics has not issued new recommendations on giving vitamin K since 2003, so intramuscular administration of vitamin K1 is still recommended

- (as recommended in 1961)

MMWR Morb Mortal Wkly Rep 2013;62(45):901-2. Pediatrics 2003;112:191-2.

Pediatrics 1961;28:501-7.

Prevention strategies for VKDB/HBN :

- The oldest (seems to be the most effective) **intramuscular** administration of **0,5 - 1 mg of vitamin K to all newborns**

- **oral** administration **of three 2 mg doses** of vitamin K1 for parenteral use or mixed micellar form of vitamin K1

- oral administration of **small doses of vitamin K1 in the daily or in weekly intervals** particularly in exclusively breastfed babies

Br J Cancer 2003;89:1228-31. Pediatrics 2003;112:191-2. Eur J Pediatr 2003;162:885-8. Acta Paediatr 2003;92:802-5. Am J Obstet Gynecol 2004;190:882-3.

Recommendations for the prophylactic vitamin K 1 administration in different countries

Country	Parenteral vitamin K 1	Peroral vitamin K 1
USA	Single dose of 0.5 to 1.0 mg im.	-
Canada	Single im. dose 0.5 mg (BW =1500g) or 1.0 mg (BW >1500g) within first 6 hours of life	If parenteral vitamin K is unacceptable for aprents then peroral 2 mg of vitamina K1 wit the first feed, 2 to 4 weeks after the fist dose, second peroral dose of 2 mg, and the third 2 mg dose after 6 to 8 weeks.
UK	1 mg im.	or 1 mg after birth and from the 2nd week to the 3 months daily dose of 50 mg of vitamin K1
Poland	Within the first 5 hours of life 1 mg Premature infants 0.5 mg, if BW <750g 0.5 mg iv.	or 2 mg after birth. Breastfed infants ≥ 34 GW from 15 days to 3 mo 150 mg, a nad ≤34 GW 25 mg of vitamin K 1 daily.

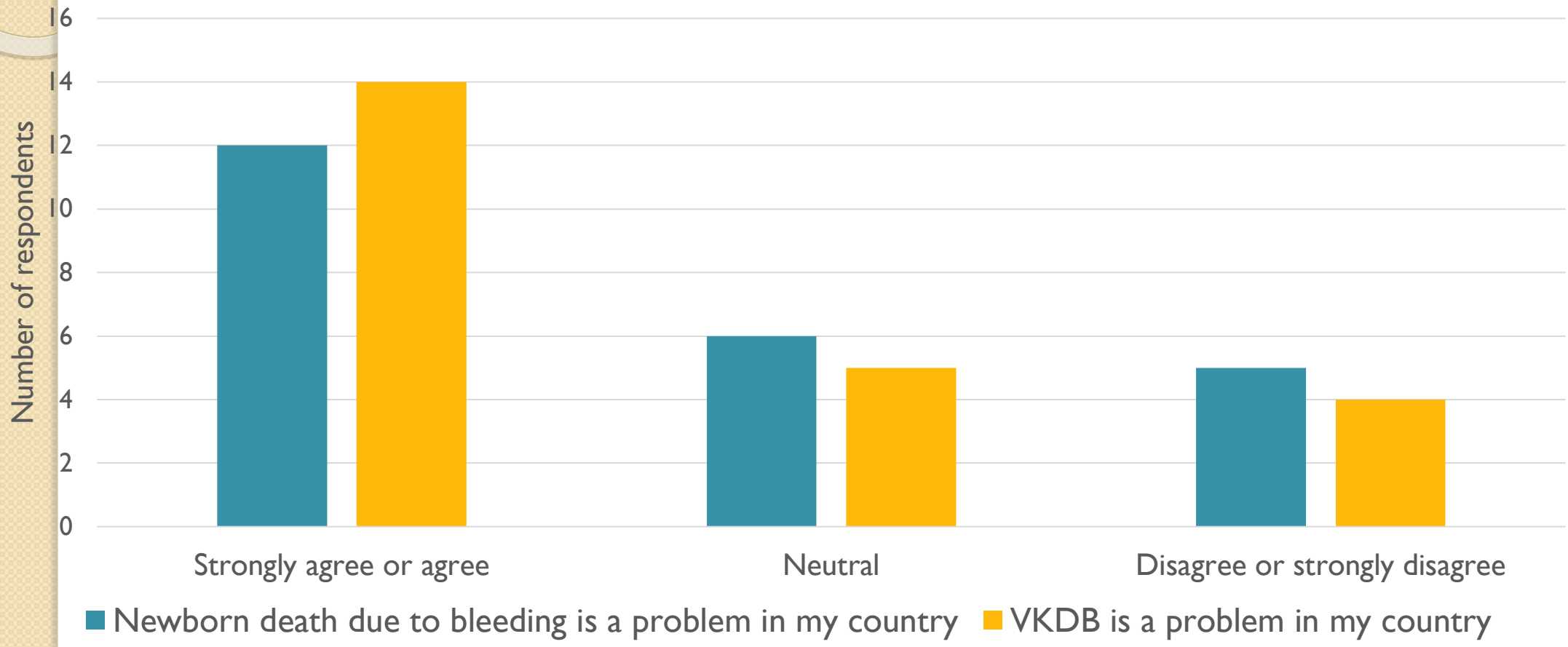
Country	Parenteral vitamin K 1	Peroral vitamin K 1
Italy	0,5 mg	or 2 mg after birth. All breastfed infants from the 2nd week to the 3rd mo 25 mg daily
Netherlands	-	1 mg vitamina K1 after birth, from the 8th day till de 13th week 25 mg daily (exclusively breastfed) to 150 mg (cholestasis) of vitamina K1 depending on the risk
Switzerland and Germany	-	2 mg of vitamina K1 after birth and at the end of the 2nd and 4th week of life
Danmark	-	1 mg after birth and then every week 1 mg of vitamin K 1 till the end of 3 months of age
Slovenia	Within 3 hours after birth 1 mg of vitamin K1	Recommending peroral use when intramuscular use is not possible
India and China	To all newborn infants after birth	-

Situation with vitamin K administration in low and middle income countries

- Prophylactic addministration of vitamin K to newborns is relatively well integrated into policy at the global and country level but its practice is underutilized
- Barriers to use are:
  - access,
  - supply chain logistics,
  - provider attitudes and
  - restriction on the use of injections by providers at the community level (many home births)

Crafey PS, Gerth-Guyette E. Current perspectives and practices of newborn vitamin K administration in low and middle income countries. Res Report Neonatol 2018;8:45-51.

Health professional perspectives on the newborn bleeding and vitamin K deficiency bleeding



Crafey PS, Gerth-Guyette E. Current perspectives and practices of newborn vitamin K administration in low and middle income countries. Res Report Neonatol 2018;8:45-51.

Policies on vitamin K administration in some developing countries

Country	Included in guidelines and policies	Administration is widely practices	Health professionals are trained
Cameroon	No	No	No
Nepal	No	No	No
Dominican Republic	Yes	Yes	Yes
Ethiopia	Yes	No	Yes
Philippines	Yes	Yes	Yes
Rwanda	Yes	Yes	Yes
South Sudan	Yes	No	No
Zambia	Yes	No	No
Zimbabwe	Yes	Yes	Yes

Crafey PS, Gerth-Guyette E. Current perspectives and practices of newborn vitamin K administration in low and middle income countries. Res Report Neonatol 2018;8:45-51.

Oral or intramuscular administration of vitamin K in the prevention of classic VKDB/HDN

- Equal efficiency of **one oral or intramuscular** dose of vitamin K1 in the prevention of classic VKDB/HDN has been proven

Peroral vitamin K administration in the prevention of late VKDB/HDN

- one oral dose of vitamin K **is not sufficient** for prevention of the **late VKDB/HDN**

- After oral administration only 30% of the vitamin K dose is absorbed

Arch Dis Child Fetal Neonatal Ed 2003;88:F113-8.

Pädiatr Prax 1989;38:629-31.

Eur J Pediatr 2003;162:885-8.

The use of vitamin K in the prevention of late VKDB/HDN

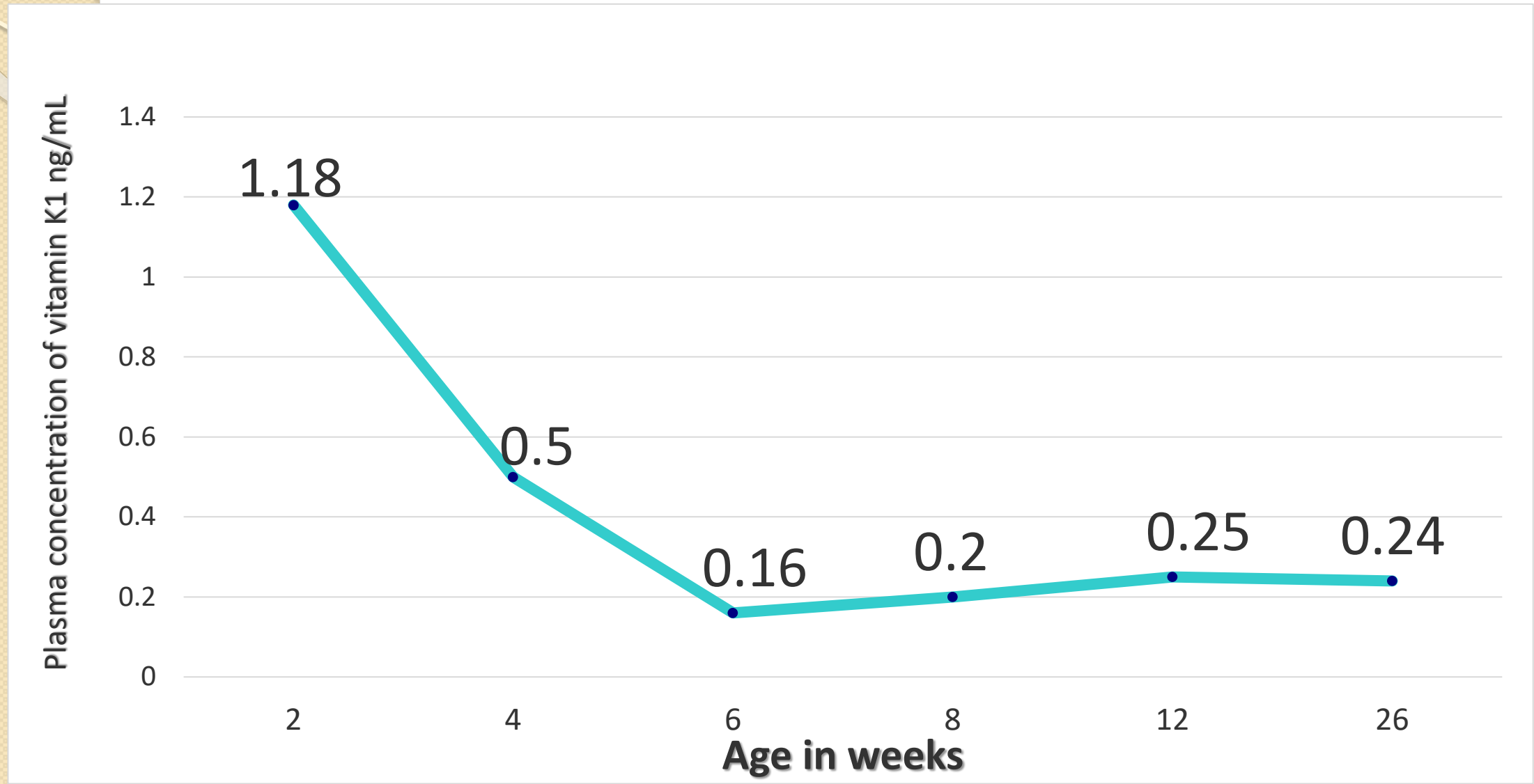
- Epidemiological research has shown that intramuscular administration of vitamin K most effective for the prevention of late VKDB/HDN

- The risk of developing late VKDB/HDN is lower after **intramuscular vitamin K 1 administration** as compared to infants who received a single oral dose of vitamin K, as well as compared to infants who had not received vitamin K prophylaxis at all

-

Arch Dis Child 1992;67:1250-4.

Plasma concentrations of vitamin K 1 in infants after intramuscular administration of a single vitamin K1 dose of 1 mg



Prophylaxis of VKDB/HDN in Croatia

- The only registered form of **vitamin K1 in Croatia is phytomenadione vials 10 mg/1 ml** for intravenous use which is administered intramuscularly.

- This vitamin K1 preparation for intravenous use is used **intramuscularly in all newborns** in accordance with the recommendations of the informal group of Croatian Pediatric Society and Croatian Society of Perinatal Medicine of Croatian Medical Association, which have been published in 1994

Pediatr Croat 1994;38:189.

Gynaecol Perinatol 1994;3:95.

Prophylaxis of VKDB/HDN in Croatia

- In the meantime, there is a need **for oral administration** of vitamin K1 in low-risk newborns
- There is **no registered vitamin K1** for oral use in Croatia, **so intravenous phytomenadione is used orally**
- It is necessary **to advocate for the registration** of vitamin K1 preparations for oral use in Croatia

Pediatr Croat 1994;38:189.

Gynaecol Perinatol 1994;3:95.

General non selective vitamin K 1 prophylaxis of VKDB/HDN introduced in Croatia:

- **All newborns** should get single intramuscular dose of **0.5 to 1.0 mg of vitamin K1 immediately** (1 to 2 hours) **after birth**. Newborns with birth weight up to 1,500 grams should receive 0.5 mg, and those of more than 1500 grams should get 1 mg of vitamin K1 intramuscularly.

- Newborn babies of parents **who refuse intramuscular** administration of vitamin K1 should be given **orally 1 to 2 mg vitamin K1** registered for intravenous use immediately (1 to 2 hours) or with the first breastfeeding

Pediatrics 2008;122(5):1142-52.

Early Hum Dev 2009;85(10 Suppl):S27-9.

General non selective vitamin K 1 prophylaxis of VKDB/HDN should be introduced in Croatia as follows:

- **Newborns at risk** should **receive from 8 days to 12 weeks of age 25 μg of vitamin K 1 and 400 IU of vitamin D 3 administered orally once a day,** in accordance with the recommendations of the American Academy of Pediatrics and other societies which are related to the use of vitamin D in all infants shortly after birth

- Infants who are **fed with breast milk substitutes** should receive vitamin K1 prophylaxis after birth, while there is no need for the prophylactic vitamin K administration in infancy.

Pediatrics 2008;122(5):1142-52. Early Hum Dev 2009;85(10 Suppl):S27-9.

Newborns at risk are:

- **Exclusively breast-fed infants** from **8 days to 12 weeks**,
- All infants who have **less than two complete meals of infant formula/daily** at the age of 8 days to 12 weeks,
- All newborns who within 1 hour after oral administration of vitamin K1 had spit up or vomited
- Newborns with **late onset** of breastfeeding
- Sverely sick newborns
- Newborns **treated more that 14 days with antibiotics** or anticoagulants from the warfarin group
- **Premature and hypotrophic infants**

Newborns at risk are:

- newborns with **birth asphyxia, intrauterine growth restriction, and meconium aspiration syndrome**
- **newborns of the mothers treated** in pregnancy with carbamazepine, phenytoin, barbiturates, cephalosporins, rifampicin, isoniazid and cumarine preparations
- infants with **proven cholestasis and prolonged jaundice** lasting more than 21 days
- infants with **diarrhea lasting more than 7 days**

Recommendations for prevention of HDN in Croatia - important facts

- According to the Croatian Institute for Public Health, the rate of exclusive breastfeeding in Croatia at the age 3 to 5 months **increased from 32% in 2007 to 46.2% in 2014**, which increases the risk of late HDN development

Hrvatski zavod za javno zdravstvo. Hrvatski zdravstveno statistički ljetopis za 2014. godinu. HZJZ: Zagreb, 2015. http://www.hzjz.hr/wp-content/uploads/2014/04/ljetopis_20141.pdf

Prophylaxis of late VKDB/HDN is recommended in Croatia as follows:

- **All newborn infants should receive 0.5 to 1.0 mg of vitamin K1 intramuscularly or 1.0 to 2.0 mg of vitamin K 1 oraly**

- **All newborns at risk** should be supplemented orally **from 8th day of life to the completed 12 weeks of life with 25 mg of vitamin K1 and 400 IU of vitamin D 3 once a day,** (According to the recommendation for vitamin D prophylaxis shortly after birth of the American Academy of Pediatrics and other pediatric societies)

Pediatrics 2008;122(5):1142-52.

Early Hum Dev 2009;85(10 Suppl):S27-9.

Historical perspective of prevention of neonatal VKDB bleeding in Croatia

Period (year)	Prophylactic use of vitamin K (percentage of newborns)
Till 1989	**25.8%** non-selective use of vit. K, **100%** im.
From 1990 to 1995	**85.9%** non-selective use of vit. K, predominantly im.
From 2017	More than **90%** im. vitamin K after birth, in 70% of high risk neonates for VKDB prolonged peroral prophylactic use of vitamin K recommended from 8 days to 12 weeks

Stanojević M, Gjurić G. Profilaksa hemoragijska bolesti novorođenčeta u Republici Hrvatskoj. Gynaecol Perinatol 1992;1:161-2.

Stanojević M, Gjurić G. Profilaksa hemoragijske bolesti novorođenčeta u Republici Hrvatskoj 1995. godine. Gynaecol Perinatol 1997;6:81-5.

ESPAGHAN recommendations on VKDB prevention

- Healthy newborn infants should either receive 1 mg of vitamin K1 by intramuscular injection at birth;
- or 3 x 2 mg vitamin K1 orally at birth, at 4-6 days and at 4-6 weeks;
- or 2 mg vitamin K1 orally at birth, and a weekly dose of 1 mg orally for 3 months.
- Intramuscular application is the preferred route for efficiency and reliability of administration.

J Pediatr Gastroenterol Nutr. 2016 Jul;63(1):123-9. doi:10.1097/MPG.0000000000001232.

ESPAGHAN recommendations on VKDB prevention

- The success of an oral policy depends on compliance with the protocol and this may vary between populations and healthcare settings.
- If the infant vomits or regurgitates the formulation within one hour of administration, repeating the oral dose may be appropriate.
- The oral route is not appropriate for **preterm infants** and for newborns who have cholestasis or impaired intestinal absorption or are too unwell to take oral vitamin K1, or those whose mothers have taken medications that interfere with vitamin K metabolism.

J Pediatr Gastroenterol Nutr. 2016 Jul;63(1):123-9. doi:10.1097/MPG.0000000000001232.

Cost effectiveness of the prevention of the late VKDB by im administration of vitamin K1

- Number needed to treat (im. vitamin K1 after birth) to prevent clinically significant late VKDB is 1275 (CI 1042 to 1667)
- If cost of one postnatal intramuscular vitamin K1 injection is 1 USD, cost of one year without disease would be 52 USD in low and middle income countries, and 133 USD in high income countries.
- According to the World Bank all procedures with cost below 100 USD per one year without disease are cost effective, which means that this pply to the late VKDB bleeding (incidence 72 per 100.000 live-born).

Sankar MJ, Chandrasekaran A, Kumar P, Thukral A, Agarwal R,Paul VK. Vitamin K prophylaxis for prevention of vitamin K deficiency bleeding: a systematic review. **J Perinatol. 2016; 36(Suppl 1): S29–S35.doi: 10.1038/jp.2016.30.**

Thank you for your attention



