INTRODUCTION

The National Health and Medical Research Council (NHMRC) Joint Statement and Interim Recommendations on Vitamin K Prophylaxis for Haemorrhagic Disease in Infancy (HDN) was endorsed by Council on 24th December 1992.

The Statement is a response to recent research conducted in the United Kingdom which suggests that intramuscular vitamin K might increase the risk of childhood cancer. An expert panel established by the Health Care Committee of NHMRC, the Australian College of Paediatrics (ACP) and the Royal Australian College of Obstetricians and Gynaecologists (RACOG), has weighed up the available evidence for the efficiency of oral vitamin K, the risk of HDN and the risk of cancer, and have made the following recommendations.

1. Vitamin K is required in the first six weeks of life to prevent a rare but potentially fatal bleeding disorder, and is effective when given by intramuscular or repeated oral doses.

2. All healthy full term infants could receive three oral doses of vitamin K, instead of a single intramuscular dose at birth. The first oral dose should be given at birth and the second at the time of newborn screening (3 to 5 days of age). The third dose should be given in the fourth week, if practical, because the onset of the disease has been reported as early as 4 weeks of age following a single oral dose. There is evidence to suggest that the first two doses are the most important.

3. Until an oral preparation with a higher bioavailability becomes available, oral doses of 1mg should be used.

4. Infants who are pre-term, unwell or unable to tolerate or absorb oral vitamin K should receive 0.1mg intramuscular vitamin K at birth followed by further doses (0.1mg intramuscularly or 1mg orally) at the time of newborn screening (3 to 5 days of age) and in the fourth week of life. The route of the second and third dose should depend on the condition of the infant, (NHMRC, Dec. 1992).

The Health Department of Western Australia has considered the recommendations of the NHMRC, and the implications for the maternal and child health care consumers and providers in the diverse settings and circumstances within WA, and it is evident that a number of options will be required to facilitate administration of the three doses of vitamin K throughout this State.

The following interim policy and protocol statement is provided for HDWA maternal and child health providers.
VITAMIN K ADMINISTRATION PROTOCOL

ALL HEALTHY FULL TERM BABIES

DAY 1
1mg (0.5ml) Konakion given orally at the time of the first feed.
If there is any concern that the first dose was not retained it should be repeated on day 2.

DAY 3, 4 or 5 (when Guthrie test performed)
1mg (0.5ml) Konakion given orally.

AT 4 WEEKS OF AGE
1mg (0.5ml) Konakion given orally.

The first dose will be given in hospital (or place of birth).
The second dose will be organised by the hospital for administration as an inpatient or outpatient
depending on local arrangements.

Presenting for the third dose will be the responsibility of the parents of the infant. It may be given at
the time of a postnatal medical check at 4 weeks, or parents may choose to have it administered by
the community nurse at 4 weeks.

PRE-TERM OR UNWELL BABIES

Babies who may be unable to tolerate the oral dose of vitamin K should receive a reduced dose of
parenteral vitamin K (Konakion). The condition of the baby will determine the best method of
administration.

INTRAMUSCULAR ADMINISTRATION
AT BIRTH
0.1mg (0.05ml) Konakion

AT 4 - 5 DAYS
0.1mg (0.05ml) Konakion

AT 4 WEEKS
0.1mg (0.05ml) Konakion

ORAL ADMINISTRATION
If 0.1mg Konakion is given intramuscularly at birth and the oral route is tolerated for the second and
third doses of vitamin K then the doses will be:

AT 4 - 5 DAYS
1mg (0.5ml) Konakion orally

AT 4 WEEKS
1mg (0.5ml) Konakion orally.

VITAMIN K SUPPLY

As there is currently no commercial vitamin K preparation licensed for oral administration in Australia
ampoules of 1mg Konakion should be used. The contents of the ampoule used for intramuscular
injection have been given orally in other countries with no adverse effect (NHMRC, 1992). Hospitals
will require additional supplies of Konakion to provide for the two doses given to each baby during the
first week. Regional pharmacies have been advised of the need for increased supplies. Orders can
be placed in the usual way. Private hospitals and medical practices can obtain supplies through
pharmaceutical wholesalers. The cost per ampoule is approximately 70 cents.

The pharmacy department at Princess Margaret Hospital for Children is preparing a supply of vitamin
K which they can dispense in containers for oral administration. Public hospitals can order supplies
of this preparation directly from PMH after the 4 week period required to manufacture supplies.
Community nurses will be able to obtain supplies of the oral preparation through their usual
pharmaceutical services. The expected cost for a 15ml (30 dose) container of the preparation for
oral administration is estimated to be $9.30c with each dose being approximately 31 cents.
For doses requiring administration before March 1st it will be necessary to use the intramuscular preparation in the ampoules. Mothers should be given an ampoule of Konakion to take to their doctors for administration during the fourth postnatal week. This will not be required after March 1st when the vitamin K for oral administration should be available.

**STORAGE**

Conditions for storage remain as per the manufacturer's instructions. Konakion is photosensitive and is dispensed in dark ampoules. It should be stored away from direct light.

To avoid duplication in ordering supplies it is recommended that liaison occurs between local health care providers and that requirements are estimated on current birth statistics and trends as documented in the Ninth Annual Report of the Western Australian Midwives' Notification System (Gee, V. 1992 p 11 - 19).

**INFORMED CONSENT**

Parents should be informed of the need for Vitamin K administration to prevent Haemorrhagic Disease of the Newborn. Their consent should be sought prior to administration.

**INFORMATION FOR PARENTS**

Medical practitioners, midwives and community nurses should inform themselves on the current research findings and subsequent changes to practice in order to provide parents with answers to questions they may raise in response to media releases related to Vitamin K administration. A copy of the background to the NHMRC Statement and Recommendations will be enclosed with this HDWA interim operational statement for circulation amongst clinicians involved in the administration of vitamin K. An information card (CHS 170) will be issued to the mother of the infant explaining the need for oral vitamin K and the procedure of oral administration. The reverse side of the card will serve as a record of the dates of administration of the three doses. This card will be available in various languages through HDWA stores. It is expected that Card CHS 170 will be available by 15 February.

**REIMBURSEMENTS AND COSTS**

The overall cost of implementing this change in practice is less than $50000 per annum. The greater percentage of this cost will be incurred in the metropolitan area (68%). Costs to the country regions will range from approximately $1000 to $4000. With such a wide dispersal of the costs amongst health services in Western Australia no additional funding will be allocated to regional budgets for this financial year.

**REFERENCES**

Gee, V. 1992, Perinatal Statistics in Western Australia, Health Department of Western Australia, Perth.

National Health and Medical Research Council, Australian College of Paediatrics, and Royal Australian College of Obstetricians and Gynaecologists, 1992, Joint Statement and Interim Recommendations on Vitamin K Prophylaxis for Haemorrhagic Disease in Infancy, National Health and Medical Council.

**BIBLIOGRAPHY**

A reference list to readings is given on Attachment 2 page 3 of the NHMRC information.
JOINT STATEMENT AND INTERIM RECOMMENDATIONS ON

VITAMIN K PROPHYLAXIS FOR HAEMORRHAGIC DISEASE IN INFANCY

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL (NHMRC)
AUSTRALIAN COLLEGE OF PAEDIATRICS (ACP)
ROYAL AUSTRALIAN COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS (RACOG)

In Australia, vitamin K prophylaxis is given routinely to almost all newborn infants to prevent a rare but potentially fatal bleeding disorder, haemorrhagic disease of the newborn (HDN), which may present during the first six months of life. Vitamin K is given by intramuscular injection in most cases.

There has long been debate about whether the less invasive oral route could be used, but evidence to date suggests that a single oral dose at birth may not prevent all cases of late haemorrhagic disease. This debate has been raised again following a study in the United Kingdom which suggests that intramuscular vitamin K might increase the risk of childhood cancer.

In response to the study, the Health Care Committee of NHMRC, the ACP and RACOG established an expert panel to advise on the continued use of intramuscular vitamin K in Australia. The panel, chaired by Professor David Henderson-Smart, had available to it the deliberations of experts in the United Kingdom, New Zealand and the United States.

The panel weighed up the available evidence for the efficacy of oral vitamin K, the risk of HDN and the risk of cancer, and drew the following conclusions:

1. The evidence that adequate prophylaxis with vitamin K prevents haemorrhagic disease of the newborn is very strong.

2. There is some epidemiological evidence for an association between intramuscular vitamin K and the subsequent development of cancer in childhood. However, this evidence comes mainly from one study which has some major weaknesses.

In making its recommendations, the panel considered:

- A non-invasive form of prophylaxis is always to be preferred.
- Any alternative regimen for preventing HDN must be practical, easy to comply with and as effective in preventing HDN as the intramuscular regimen.
- A single dose of oral vitamin K effectively protects against bleeding due to vitamin K deficiency in the first two weeks of life but is less effective at protecting against late onset HDN which may present with intracranial haemorrhage.
- There is currently no vitamin K preparation licensed for oral administration in Australia. The contents of the ampoule used for intramuscular injection have been given orally in other countries with no adverse effect.
- The mechanism for any potential carcinogenic effect of the intramuscular vitamin K preparation is not known (i.e. whether it is the vitamin K itself or another
constituent, and what dose is required to initiate cancer).

Despite reservations about the methodology of the British study, the expert panel was of the view that the study findings should not be ignored and that a non-invasive form of prophylaxis should be preferred where possible.

On the basis of available evidence, the panel recommends:

1. Vitamin K is required in the first six weeks of life to prevent rare but potentially fatal bleeding disorder, and is effective when given by intramuscular or repeated oral doses.

2. All healthy full term infants could receive three oral doses of vitamin K, instead of a single intramuscular dose at birth. The first oral dose should be given at birth and the second at the time of newborn screening (3 to 5 days of age). The third dose should be given in the fourth week, if practical, because the onset of the disease has been reported as early as 4 weeks of age following a single oral dose. There is evidence to suggest that the first two doses are the most important.

3. Until an oral preparation with a higher bioavailability becomes available, oral doses of 1 mg should be used.

4. Infants who are pre-term, unwell or unable to tolerate or absorb oral vitamin K should receive 0.1 mg intramuscular vitamin K at birth followed by further doses (0.1 mg intramuscularly or 1 mg orally) at the time of newborn screening (3 to 5 days of age) and in the fourth week of life. The route of the second and third dose should depend on the condition of the infant.

The panel recommends that further research be undertaken into:

- the most suitable oral regimen;
- the pharmacology of vitamin K by oral and intramuscular routes; and
- the potential carcinogenicity of vitamin K preparations including all constituents.

The panel also recommends that national epidemiological surveillance of cases of HDN and childhood cancer should be undertaken.

These interim recommendations should be reviewed as further information becomes available.

Statement endorsed by Council 24/12/92
BACKGROUND TO THE STATEMENT AND INTERIM RECOMMENDATIONS
ON VITAMIN K PROPHYLAXIS IN INFANCY

THE PROBLEM

- Virtually all infants in Australia receive an injection of vitamin K at birth to prevent a potentially serious bleeding disorder, haemorrhagic disease of the newborn (HDN), which is due to vitamin K deficiency. The intramuscular route has been preferred because a single injection effectively prevents all forms of HDN.

- In August 1992, the British Medical Journal published a case-control study (Golding i et al 1992) which suggests that infants given intramuscular vitamin K at birth are around twice as likely to develop cancer before the age of 10 as infants not given vitamin K by the intramuscular route (odds ratio 1.97; 95% confidence interval 1.28 to 3.04; p=0.002).

NMMC RESPONSE

- The Golding study was brought to Health Care Committee’s attention at its meeting in September 1992.

- HCC referred the issue to Child Health Committee, which subsequently asked Professor David Henderson-Smart (neonatologist) to develop an appropriate response to the issue.

- Professor Henderson-Smart brought together a group including representatives of the Australian College of Paediatrics (ACP) and the Royal Australian College of Obstetricians and Gynaecologists (RACOG). The membership of this group is at attachment 1.

- The group reviewed the Golding study, and considered the available literature and the views of experts in the United Kingdom, New Zealand and the United States. Subsequently, the group drafted a statement and interim recommendations on vitamin K prophylaxis in Australia.

- There has been consumer representation on each of the NHMRC groups involved. Professor Colin Binns, chair of the NHMRC Infant Nutrition Working Party has also had input to the statement.

ISSUES

The following issues were discussed by each group involved in the development and endorsement of the statement on vitamin K prophylaxis:

1. Importance of the Golding study

- It is generally acknowledged that the Golding study has flaws which may have biased the results. Despite this, epidemiologists in the UK and those involved in the development of the statement are almost unanimous in saying that the results cannot be ignored.
The results of the Golding study cannot be quickly or easily 'proven' by clinical trial.

The clinicians and epidemiologists involved in the development of the statement agree that it is unlikely that the intramuscular route would have been recommended if the possibility of an association with childhood cancer had been known at the time routine prophylaxis was introduced.

2. The efficacy of oral vitamin K

There is generally a lack of information about the pharmacology of vitamin K.

A summary of the readily accessible evidence indicating the efficacy of oral vitamin K in the prevention of HDN is at attachment 2.

There is inadequate information about the appropriate dose and timing for an oral regimen. It is also not clear whether the association with cancer is due to the high blood levels following intramuscular vitamin K or some other constituent of the injection (e.g. phenol). The general consensus is that the oral route allows for more effective detoxification and that two to three oral doses of 1 mg each should provide adequate but not excessive blood levels of vitamin K.

Infants who are unable to tolerate oral vitamin K will continue to need intramuscular prophylaxis at birth, but the panel recommends that they be given a greatly reduced dose.

3. Lack of a suitable oral preparation in Australia

Vitamin K is currently only marketed for parenteral use in Australia. It is expected that an application will be submitted to the Therapeutic Goods Administration early in 1993 to market an oral preparation, however such approvals usually take 6 to 12 months.

The intramuscular preparation has been given orally in the UK and other countries for some time with no reports of adverse consequences (McNinch A et al, Arch Dis Child 1985, 60:814-818; Allen A, CMAJ 1989, 140:13; McNinch A and Tripp J BMJ 1991, 303:1105-9).

4. Routine versus selective prophylaxis

While certain risk factors for HDN have been identified (primarily prematurity, perinatal complications, antibiotic administration, gastrointestinal and liver disturbances, and breastfeeding) it is not possible to accurately predict all babies who will develop HDN.

Any recommendation which might discourage breastfeeding is seen as highly undesirable.

RESPONSES BY OVERSEAS EXPERTS

The British government established an expert panel to examine and recommend on the implications of the Golding study. The panel included Dr Golding, representatives of the British Paediatric Association, and experts from several European countries. The panel has not reported yet, but a confidential draft report was available to the NHMRC panel. This draft recommended that all healthy infants should receive 0.5 mg vitamin K orally at birth and that breastfed infants should be given two subsequent doses of 0.5 mg orally at 7-10 days and 4-6 weeks of age.
• The Fetus and Newborn Committee of the Paediatric Society of New Zealand has recently made similar recommendations but suggests that a 2 mg dose be used.

• The Canadian Paediatric Society recommended in 1988 that healthy term infants could be given either 1 mg intramuscularly or 2 mg orally at birth. Similar recommendations were made by the American Academy of Paediatrics at the same time. No changes to these recommendations have been published to date.

REASON FOR URGENCY

• There is considerable concern amongst paediatricians and obstetricians about the implications of the Golding study. The Colleges and the NHMRC secretariat have had numerous calls from doctors wanting to know what action they should take.

• Health departments in most states are waiting for guidance from the NHMRC and the Colleges on whether or not they should change their current policies on vitamin K prophylaxis.

• Some practitioners and hospitals have already decided to change to the oral route and are using varying regimens. This is undesirable as monitoring will be very difficult.

PROPOSED DISSEMINATION STRATEGY

• The first phase of the strategy involves dissemination of the statement to the profession through the ACP, RACOG, the Royal Australian College of General Practitioners, state health departments, private maternity hospitals, the Health Insurance Commission and the medical media (Australian Doctors Weekly and Medial Observer).

• The second phase of the strategy involves public release of the statement to inform prospective parents. A press release for this purpose will be made on 20 January 1993.

PROPOSED MONITORING AND REVIEW ARRANGEMENTS

• It has been suggested that the newly established Australian Paediatric Surveillance Unit and the AIHW's National Perinatal Statistics Unit should be requested to undertake surveillance of HDN to monitor the change from intramuscular to oral prophylaxis.

• The HCC secretariat will monitor the literature and keep Child Health Committee informed of any relevant new studies.

• MRC and PHRDC could consider supporting research into the areas noted in the statement. Research to determine the most appropriate oral regime could be commissioned through the Priority Research Fund.
MEMBERSHIP OF EXPERT GROUP ON VITAMIN K PROPHYLAXIS

Prof David Henderson-Smart (Chair)  expert in neonatology
Dr Elizabeth John  representative of the Australian College of Paediatrics
Dr Colin Fisher  representative of the Royal Australian College of obstetricians and Gynaecologists
Dr Michael Frommer  Epidemiologist
Dr Elizabeth Murphy  expert in child health
Dr Doris Zonta  NHMRC secretariat
VITAMIN K - SUMMARY OF EVIDENCE REGARDING ORAL USE

There is clear evidence that a single oral dose adequately protects against early (day 1) and classical (week 1) haemorrhagic disease of the newborn (HDN) (O'Connor et al 1986, Jorgensen et al 1991).

The following evidence is available about late HDN (after the first week of life) and the use of oral vitamin K:

Cornelissen et al 1992
- 331 healthy breast-fed infants randomly allocated to receive 1 mg vitamin K orally or 1 mg intramuscularly on the first or second day of life. Vitamin K, clotting factors and proteins induced by vitamin K absence (PIVKA-II) measured at 2 weeks, 1 month and 3 months.
  - vitamin K concentrations in the oral prophylaxis group were lower at all ages.
  - there were no differences in blood coagulability or clotting factor activity between the two groups at any age (Mann-Whitney, P>0.05)
  - PIVKA-II were not detectable in any infants at 2 weeks of age; differences between the two groups were detected at 1 month and 3 months of age but were not statistically significant.
  - PIVKA-II levels at 1 and 3 months suggest that oral vitamin K is no longer completely effective by 4 weeks, and intramuscularly vitamin K is no longer completely effective by 3 months

von Kries et al 1992
- Survey of cases of late HDN presenting to all paediatric hospitals in West Germany (n=225). Response rate 85%. 14 cases reported between 1/1/88 and 30/3/89 out of an estimated 750,000 live births.
  - incidence of late HDN:
    1 in 14,000 for no prophylaxis
    1 in 70,000 for single oral dose (1-2 mg)
    1 in 420,000 for single i.m. dose (1 mg)
  - relative risk of late HDN associated with single oral dose compared to single intramuscular dose was 5.97 (95% confidence interval 0.5 to 65.8)
  - The difference in the efficacy of a single oral dose and a single intramuscular dose was not significant (p=0.157, Fisher’s exact test)
McNinch and Tripp 1991

- prospective survey of HDN in Britain and Ireland from December 1987 to March 1990
- 27 cases detected, of which 20 had had no prophylaxis and 7 had had a single oral dose. All cases following oral vitamin K were late HDN, with mean age at presentation 5.9 weeks (range 4 to 8.5 weeks).
- Relative risk of HDN after single oral dose was 13.4 (95% confidence interval 1.65 to 109)

Hathaway et al 1991

- 56 breast-fed infants randomly assigned to receive 5 mg orally, 2 mg orally or 1 mg intramuscularly during the first 4 hours of life. 10 infants who received no vitamin K and 20 healthy adults (aged 20 to 40) were used as controls. Plasma vitamin K and PIVKA-II measured at 4 weeks
- mean plasma vitamin K levels at 4 weeks of age were similar to adult values in all treated groups, however, there were more infants with low plasma levels in the groups which had received oral vitamin K than in the group which received intramuscular vitamin K
- PIVKA-II were slightly but significantly elevated at 4 weeks of age in all treatment groups, regardless of route, compared to adult controls (p=0.05)
- cite Hanawa et al (1990): in Japan 2 mg vitamin K is given orally 1 to 3 times during the first 2 weeks of life; the incidence of late HDN has decreased remarkably and is now seen only in those infants given a single oral dose

Note: the rate of late HDN in Japan was reported in a recent (untranslated study) to be 2 per 100,000 provided 3 oral doses are given (personal communication, Dr Elisabeth John)


- 19029 infants screened for PIVKA-II at 1 month of age
- 2 mg vitamin K given orally within the first 24 hours of life did not significantly reduce the PIVKA-II detection rate
- those infants given a second 2-4 mg dose on day 5 still had high PIVKA-II levels at 1 month
- proportion with high PIVKA-II levels:
  - overall 0.27%
  - solely breastfed, no prophylaxis 0.51%
  - 2-4 mg orally on day 1 0.36%
  - 2-4 mg orally on days 1 and 7 0.19%
REFERENCES

Cornelissen EAM, Kollee LAA, De Abreu RA, van Baal JM, Motohara K et al 1992, 'Effects of oral and intramuscular vitamin K$_1$, prophylaxis on vitamin K PIVKA-II, and clotting factors in breast-fed infants', Archives of Diseases in Childhood, 67: 1250-54


