ORIGINAL ARTICLE

# Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993–94 and 2001–02

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**Objective:** To conduct and report monitoring of vitamin K deficiency bleeding (VKDB) in Great Britain and Ireland following the 1988–90 survey (VKDB-90).
**Design:** Two 2-year surveys conducted during 1993–4 (VKDB-94) and 2001–02 (VKDB-02).
**Setting:** Data collected from all consultant paediatricians in Great Britain and Ireland.
**Patients:** All infants presenting with bleeding resulting from vitamin K (VK) deficiency.
**Main outcome measures:** Incidence of VKDB, related mortality/morbidity and VK prophylaxis recommended/received, noting predisposing features.
**Results:** Compared with previous studies, VKDB-02 found fewer cases of VKDB (RR: 0.27 (95% CI: 0.12 to 0.59), $p<0.001$) with no deaths, no long-term morbidity and reduced incidence among those receiving any oral dosing (RR: 0.24 (95% CI: 0.06 to 1.01), $p<0.059$). Breast-fed infants accounted for the vast majority of cases. The number receiving no prophylaxis fell consecutively over time: 20 of 27 in VKDB-90, 10 of 32 in VKDB-94 and 4 (because of parental refusal) of 7 in VKDB-02. Seven received one oral dose of VK in VKDB-90, 16 in VKDB-94 and none in VKDB-02. Underlying liver disease was found in six cases in VKDB-90, 12 in VKDB-94 and one in VKDB-02.
**Conclusions:** In the most recent survey, the incidence of VKDB was about one third that in the two earlier studies. Late onset VKDB remains virtually confined to breast-fed infants who have received either no VK or just one oral dose. The effectiveness of oral prophylaxis regimens has improved over the last 15 years, but parental refusal of prophylaxis has become more problematic.

At the time of the first prospective survey of vitamin K deficiency bleeding (VKDB) in Great Britain and Ireland (1988–90), some 60% of neonates were offered intramuscular (IM) vitamin K (VK) prophylaxis and 30% an oral regimen.[1] Konakion Neonatal (Roche, Basel, Switzerland), containing Cremophor EL as the solubilising agent, was the single available preparation and was licensed only for parenteral use. Of the 27 cases of VKDB, 20 had received no prophylaxis and seven oral VK; 24 were exclusively breast fed; liver disease was identified in seven; in 14 there was a delay (1–14 days) between the first bleeding manifestation and presentation to hospital; 10 had intracranial haemorrhage (ICH), six of them after ''warning bleeds'' of 1–14 days' duration; and of those with ICH, two died and all others suffered significant sequelae.[2]

The report emphasised the need for VK prophylaxis for all newborns, repeated doses in breast-fed infants given oral prophylaxis, early investigation of babies with evidence of cholestasis and emergency investigation of ''warning bleeds''.[3] To monitor progress, two further 2-year prospective surveys were conducted by the same methods in the same study area; all three surveys were carried out under the auspices of the British Paediatric Surveillance Unit (BPSU). In this paper the surveys are referred to as VKDB-90, VKDB-94 and VKDB-02; the findings of VKDB-94 (1993–4) and VKDB-02 (2001–02) are reported.

Cases of VKDB are conventionally divided into three groups according to age at onset of bleeding: ''early'' (onset within 24 h of birth), ''classical'' (onset 1–7 full days after birth) and ''late'' (onset after 7 days). Although somewhat arbitrary, these groupings are helpful in considering aetiology, mode of presentation and prophylaxis,[4] and so are used in this report.

## METHODS

Cases were recruited by means of the well-described BPSU methodology as in VKDB-90.[2] ''Vitamin K deficiency bleeding'' was included among the reportable conditions between January 1993–December 1994 and January 2001–December 2002 inclusive. Paediatricians in Great Britain and Ireland were asked to report all possible cases, defined as: ''Any infant under 6 months of age with spontaneous bruising/bleeding or ICH associated with prolonged clotting times, not due to an inherited coagulopathy or disseminated intravascular coagulation''. The questionnaires requested details of maternal medication, pregnancy and delivery, birth weight, VK prophylaxis, type of feeding, the site/timing of bleeding, investigations, treatment and outcome. Cases were classified, according to the same criteria used in VKDB-90, as ''confirmed'' (appropriate history of bleeding, documented prothrombin time or INR at least twice the control value, platelet count normal or raised, no evidence of infection/disseminated intravascular coagulation), ''probable'' (appropriate history of bleeding, diagnosis other than VKDB unlikely but lacking full laboratory confirmation), ''duplicate'' (already notified), ''no case'' (criteria not met) or ''error''.

A report in 1997[5] compared incidences of late VKDB from the Netherlands, Germany, Australia and Switzerland and related them to different prophylaxis policies. It used case definition criteria, agreed internationally in 1994,[5] which were more exclusive than those of the BPSU studies (above) devised by us in 1987 for the first study. For comparison with these data from

**Abbreviations:** BPSU, British Paediatric Surveillance Unit; ICH, intracranial haemorrhage; IM, intramuscular; VK, vitamin K; VKDB, vitamin K deficiency bleeding

other countries, the cases of late VKDB reported to the BPSU studies were re-classified according to these stricter criteria.

Birth statistics were obtained from the appropriate national bodies.

Concurrent surveys of prophylaxis practices in the United Kingdom and Ireland are reported elsewhere.[6 7]

## RESULTS

During the two study periods, 93.1% and 92.5% of the BPSU monthly report cards were returned, demonstrating excellent cooperation from paediatricians in the study area.

### Notifications and classification

#### VKDB-94

There were 111 notifications; 103 questionnaires were returned yielding 30 confirmed and two probable cases, 13 duplicates, and 58 ''no case'' or ''error'' reports. Both probable cases suffered ICH but had relatively minor prolongation of clotting times; in case 4 excessive birth weight and difficult delivery may have caused the bleeding.

#### VKDB-02

There were 42 notifications; 39 questionnaires were returned yielding seven confirmed and no probable cases, five duplicates and 27 ''no case'' or ''error'' reports.

The data summarised below and detailed in tables 1 and 2 refer to confirmed and probable cases combined.

### Delivery, birth weight, feeding and gender

#### VKDB-94 (n = 32)

There were 17 boys and 26 were born by normal delivery. Case 31 was born at 32 weeks' gestation and all others were born at term. Median birth weight was 3.4 kg (range 2.2–4.7 kg). Three babies were formula fed (soy formula in two), two had mixed feeds, 25 were solely breast fed, one predominantly so and one was unfed.

#### VKDB-02 (n = 7)

All were born at term (gestation $37^0$-$41^6$ weeks) and weighed 2.5–4.0 kg (neither gender nor exact weight were requested, to reduce data risks). One baby was predominantly formula fed (soy) and six solely breast fed.

### Vitamin K prophylaxis

#### VKDB-94

Ten received no VK prophylaxis, which was due to error in three cases, parental refusal in four (in one the recommendation was for IM prophylaxis, in three it was for oral prophylaxis) and because it apparently was not offered in three. Sixteen were thought to have received one oral dose of VK (1 mg in 11 cases, 0.5 mg in four, not stated in one). Two received two oral doses and two others three oral doses (each 1 mg). Two received a single IM dose: 1 mg in case 27 and 100 μg in case 31.

#### VKDB-02

Four received no VK because parental consent was withheld (in each case the hospital recommendation was for IM prophylaxis; in at least three of the hospitals it was policy to offer oral VK as an alternative). Case 7 had two oral doses (1 mg, days 1+7) whilst breast fed; case 6 ''probably'' had three oral doses (Konakion Neonatal, 1 mg at birth, 0.5 mg at 1 week and at 1 month); case 3 received 1 mg IM at birth.

### Incidence of bleeding

In VKDB-02 the overall incidence of bleeding was significantly less than in the previous studies (RR: 0.27 (95% CI: 0.12 to 0.59), $p<0.001$) and the incidence among those receiving any oral prophylaxis regimen was lower (RR: 0.24 (95% CI: 0.06 to 1.01), $p<0.059$).

### Other medication

Four babies in VKDB-94 and one in VKDB-02 had received medication other than vitamins before presentation but in none was this considered relevant.

### Age at bleeding

#### VKDB-94

Three first bled within 24 h of birth (''early VKDB''; two received oral VK, the other none) and three between 24 h and 7 days (''classical VKDB''; none received prophylaxis). Twenty six, including all ''confirmed'' cases suffering ICH, first bled after 7 days of age (''late VKDB'').

#### VKDB-02

There was no case of ''early VKDB''. Five had ''classical VKDB'', including one with gastrointestinal bleeding on day 2 despite documentation of IM VK 1 mg at birth (see Discussion). Case 6 (''probably'' three oral doses of VK) presented at 41 days with a 2-day history of bruising; non-accidental injury was considered until abnormal clotting was found and biliary atresia was later diagnosed. Case 7 (two oral doses of VK) bled at 8 weeks and was later found to have cystic fibrosis.[8]

### Warning bleeds and delayed presentation

#### VKDB-94

Presentation was delayed by 1–2 days in six cases. Eight others had ''warning bleeds'' for 1–7 days (median 2) at one or more sites before presenting with bleeding elsewhere. Warning bleeds included bruising (seven cases), gastrointestinal bleeding (four), oozing from scratches (two), nose bleeds (two) and umbilical oozing (one). Of 10 babies suffering ICH, five had warning bleeds (bruising in three) of 1–4 days' duration.

#### VKDB-02

Two cases presented after delays of 2 days (bruising) and 6 days (nose bleeds and bruising).

### Breast feeding

Bleeding among those breast fed was significantly less common in VKDB-02 than in the two earlier studies combined ($p<0.01$, assuming breast feeding rates of 40–60%).

### Liver disease

#### VKDB-94

Liver function was tested in 29 of the 32 cases; in 14 it was normal and in one other probably so. Two had significantly raised gamma glutamyl transferase and alanine transferase but normal bilirubin and are not counted as having liver disease. Twelve had proven liver disease with diagnoses of biliary atresia (four cases), α1 anti-trypsin deficiency (three), non-specific hepatitis (two), galactosaemia (one), Alagille syndrome (one) and choledochal cyst (one). In only one baby was liver disease suspected before presentation with bleeding. Eleven of the 12 had serum bilirubin measured within 2 days of presentation; median total bilirubin was 122 μmol/l (range 50–208) and median conjugated bilirubin 84 μmol/l (40–127, n = 10); the conjugated fraction represented a median of 64% (38–100%) of the total. Eight of the nine aged >3 weeks would have been clinically jaundiced (bilirubin 70–160 μmol/l).

#### VKDB-02

One had liver disease (biliary atresia) with total bilirubin 118 mol/l and conjugated bilirubin 65 μmol/l, 2 days after presentation with bruising.

**Table 1** Clinical features of the confirmed (n = 30) and probable (cases 4 and 22) cases of VKDB notified to the 1993–94 incidence survey (VKDB-94)

| Case no. | VK prophylaxis and timing* | Feed type | Age at onset | Age at presentation | Sites of bleeding at presentation | Warning bleed sites and duration or delay in presentation (days) | Other comments | PT (control) or INR† | APTT (control)‡ | Liver problem (bilirubin (SBR) and conjugated fraction, μmol/l) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Oral 1 mg D1 | Nil | At birth | 3.5 h | Scalp electrode site | – | | 103 | 175 | No | No concern |
| 2 | Oral 0.5 mg D1 | Breast | 16 h | 24 h | Nose, scalp electrode site | GI (8 h) | | >60 | 120 | No | No concern |
| 3 | Nil | Breast | 24 h | 24 h | Nose | – | | INR 3.5 | 63 | – | No concern |
| 4 | Nil | Breast | 2.5 days | 3 days | ICH | – | Difficult delivery (see text) | 32 (13) | 52 (33) | No | Microcephaly, poor vision, floppy |
| 5 | Nil | Breast+ 25 ml formula | 2 days | 3 days | GI | (1) | | 49 (13–20) | 46 (27–38) | No (242, conj 13) | – |
| 6 | Nil | Breast | 3 days | 3 days | GI | – | Malrotation/ volvulus | 27 (12) | 63 (33) | No | – |
| 7 | Oral 1 mg probably given D1 | Breast | 11 days | 11 days | Vomited fresh blood | – | | >500 | >500 | Biliary atresia (208, conj 99) | Kasai operation 6 weeks |
| 8 | Probably nil | Breast | 13 days | 13 days | Umbilicus | – | Exchange transfusion×2 for rhesus disease | 92 (12) | 202 (43) | No | – |
| 9 | Nil | Breast | 14 days | 14 days | Skin, umbilicus | – | Severe failure to thrive | >120 | >120 | Galactosaemia (146, conj 95) | Normal development at 15 months |
| 10 | Oral 1 mg D1, D3, D10 | Breast | 15 days | 15 days | Umbilicus | – | Oedema at 9 days, Fallot's tetralogy | >200 | >200 | Alagille syndrome | – |
| 11 | Nil | Breast | 17 days | 19 days | Bruising | (2) | | >180 | >180 | No | – |
| 12 | Oral 1 mg D1, D6 | Breast | 24 days | 25 days | GI, haematuria | Bruising (1) | | >170 | >190 | α1 Antitrypsin deficiency (108, conj 94) | No concern |
| 13 | Oral D1 probably given | Breast+ formula | 28 days | 28 days | Umbilicus | – | Jaundice, failure to thrive | INR 1.8 | – | α1 Antitrypsin deficiency (118, conj 74) | – |
| 14 | Oral D1, D21 | Breast | 28 days | 30 days | Post circumcision | (2) | Haemoglobin 6.9 g/dl | INR>10 | 120 (38) | No | – |
| 15 | Oral 0.5 mg D1 | Breast | 28 days | 34 days | Haemothorax | Bruising, nose bleed (7) | Pale stools at times | >300 | >300 | Biliary atresia (127, all conj) | – |
| 16 | Nil | Breast | 30 days | 32 days | Bruising | Blood in vomit (2) | | >120 | >120 | No | – |
| 17 | Oral 1 mg D1 | Breast | 32 days | 33 days | ICH | Bruising (1) | | >100 | >300 | No | – |
| 18 | Oral 1 mg D1 | Breast | 33 days | 36 days | ICH | Umbilicus, nose bleeds (3) | Nose bleeds at 4 weeks, resolved | >60 | >120 | Biliary atresia (160, conj 107) | Shunt for hydrocephalus |
| 19 | Oral 1 mg D1 | Breast | 35 days | 39 days | ICH | Bruising (4) | | >180 | – | Biliary atresia (122, conj 72) | Mild hemiparesis |
| 20 | Oral l mg D1 | Breast | 36 days | 39 days | Nose bleed | Bruising (3), scratch oozing (1) | | >120 | 203 | No | Discharged well |
| 21 | Oral 0.5 mg ?D1 only | Breast | 39 days | 39 days | Bruising | | Forceps delivery, admitted to neo-natal unit twice | >120 | >180 | Non-specific hepatitis (135, conj 51) | – |
| 22 | Probably nil | Breast | 39 days | 39 days | ICH | | | 24 (11–15) | 51 (29–39) | No | Severe cerebral atrophy and fits |
| 23 | Oral 1 mg D1 | Breast | 43 days | 43 days | Bruising, ICH | – | | >200 | 193 | α1 Antitrypsin deficiency (50) | Hydrocephalus shunt, hypotonia |
| 24 | Oral 1 mg D1 | Breast | 45 days | 46 days | ICH, puncture sites | GI (1) | | >120 | >180 | Non-specific hepatitis (62, conj 53) | Normal at 3 years |
| 25 | Oral 1 mg D1 | Formula | 46 days | 48 days | Ooze from scratch | (2) | | 50 (<17) | 131 (<45) | Normal | – |

**Table 1** Continued

| Case no. | VK prophylaxis and timing* | Feed type | Age at onset | Age at presentation | Sites of bleeding at presentation | Warning bleed sites and duration or delay in presentation (days) | Other comments | PT (control) or INR† | APTT (control)‡ | Liver problem (bilirubin (SBR) and conjugated fraction, μmol/l) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | Oral 1 mg D1 | Soya formula | 49 days | 50 days | ICH | Bruising (1) | Shocked, haemoglobin 3.2 g/dl, ?co-lipase deficiency | >120 | >180 | SBR normal, AST 43 U/l (ref 18–28) GGT 251 U/l (ref 7–33) | Abilities within normal at 4 years Continued lipase supplements |
| 27 | IM 1 mg D1 | Soya formula | 51 days | 51 days | ICH | – | – | 150 | 230 | – | Severe brain damage, died at 2 years |
| 28 | Oral 1 mg D1 +2 further doses | Breast | 60 days | 60 days | Bruising | – | Cystic fibrosis diagnosed at 5 months | 141 | 146 | Gamma GT 35 U/l (ref 3–28), SBR 7, liver thought normal | – |
| 29 | Oral 0.5 mg D1 | Breast+ formula | 69 days | 70 days | GI | (1) | Diarrhoea, poor feeding, Hb 5.5 g/100 ml, multiple food intolerances | >160 | 138 | SBR 22, ALT 91, gamma GT 129 IU/l | – |
| 30 | Nil | Breast | 80 days | 80 days | Bruising, ICH | – | Failure to thrive | >180 | >180 | No | Normal at 14 months |
| 31 | IM 100 μg D1 | Breast | 111 days | 112 days | GI | (1) | Birth weight 2.2 kg at 32 weeks' gestation | 152 | 195 | Choledochal cyst (70, conj 40) | Well at 13 years |
| 32 | Oral D1 | Breast | 120 days | 120 days | Bruising | – | – | 31 (15) | 45 (28) | – | – |

*D1, single dose on day 1; D1, D6, 2 doses on days 1 and 6; †PT, prothrombin time in seconds (and control time) or INR (international normalised ratio); ‡APTT, activated partial thromboplastin time in seconds (and control time). GI, gastrointestinal; ICH, intracranial haemorrhage; IM, intramuscular; SBR, serum bilirubin.

**Table 2** Clinical features of the cases of VKDB (n=7, all confirmed) notified to the 2001–02 incidence survey (VKDB-02)

| Case no. | Prophylaxis | Hospital policy | Consent withheld? | Feed | Age at onset | Age at presentation | Sites of bleeding at presentation | Warning bleed or delay in presentation and duration | Other comments | PT in seconds (control) or INR | APTT in seconds (control) | Liver problem (bilirubin at presentation (μmol/l) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Nil | IM (or oral) | Yes | Breast | 34 h | 34 h | Blood in vomit and nasogastric aspirate | No | Not believed to have swallowed maternal blood | 30.7 (13.3) | 34.8 (32) | | Well |
| 2 | Nil | IM (or oral) | Yes | Breast | 42 h | 47 h | Rectal | No | Campylobacter in stools of mother and baby | 65 (12) | 53 (33) | No | Well |
| 3 | IM 1 mg | IM | No | Breast | 2 days | 2 days | Rectal bleeding | No | | 42 | 37 | Not tested | Well |
| 4 | Nil | IM (or oral) | Yes | Breast | 56 h | 56 h | Small blood loss from umbilicus, blood in naso-gastric aspirate | No | | 36 | 47 | No | Well |
| 5 | Nil | IM | Yes | Breast (poor) | 7 days | 7 days | Circumcision wound | Bled for 6 h after circumcision | Hypernatraemic dehydration at presentation | INR 2.9 | 43.8 | Not tested | Well |
| 6 | Probably multiple oral | Multiple oral | No | Breast | 39 days | 41 days | Bruising on palm of one hand | 2 days' delay | Non-accidental injury initially considered | 159 (13) | 135 (30) | Yes (total 118, conj 65) | Biliary atresia |
| 7 | Oral 1 mg on days 1 and 7 | Multiple oral | No | Formula (soy) | 62 days | 68 days | Skin bruises, nose bleed, vaccination site | Nose, 6 days | Bruising/ vaccination site – 5 days | INR>10 | 109 (<34) | No | Found to have cystic fibrosis |

APTT, activated partial thromboplastin time; IM, intramuscular; INR, international normalised ratio; PT, prothrombin time.

### Other predisposing factors

#### VKDB-94

Apart from those babies with liver disease and one requiring exchange transfusion for rhesus isoimmunisation, eight had recognised causes for VK deficiency or bleeding. Three bled only at sites of trauma (scalp electrode, circumcision, skin scratch), three failed to thrive before presentation (one subsequently thrived, one was found to have cystic fibrosis and one had probable lipase/co-lipase deficiency); the ICH in case 4 was associated with a difficult delivery and the gastrointestinal bleeding in case 6 with bowel volvulus.

#### VKDB-02

Two had intestinal bleeding alone: one had campylobacter infection and the other a nasogastric tube. One was found to have cystic fibrosis.[8] One bled only after circumcision; he had breastfed poorly and also had hypernatraemic dehydration on presentation with bleeding.

#### VKDB-94 and VKDB-02

In the two surveys together, six babies first bled within 48 h of birth; in none was a maternal drug implicated (no medication apart from iron and vitamins in 5 cases, and no information for case 1, VKDB-94).

### Outcome

#### VKDB-94

There are no follow-up data for 17; all are presumed, from their mode of presentation, to have survived unharmed. Eight were reported to have suffered no sequelae, including three who suffered ICH. Long-term sequelae were reported in six, all of whom had suffered ICH: two required shunts for hydrocephalus; one had microcephaly, poor vision and hypotonia; one had severe cerebral atrophy and fits; one brain damaged child died from chest infection at 2 years of age; and one was well at 5 years of age with very mild hemiparesis.

#### VKDB-02

No baby died and there were no sequelae from bleeding.

#### VKDB-90, VKDB-94 and VKDB-02

All reported adverse outcomes in the three studies were confined to babies who suffered ICH; details are compared in table 3.

### Late VKDB and international comparisons

The data for late VKDB in Great Britain and Ireland, reclassified by more exclusive international criteria,[5] are presented in table 4. They confirm a significant reduction in incidence in the latest survey and suggest that the various regimens of multiple-dose oral prophylaxis currently used do give effective prophylaxis against late bleeding. Overall rates are comparable to those reported from other European countries.[5 9]

## DISCUSSION

The aim of these studies was to learn more about VKDB, to document the effectiveness of VK prophylaxis and to attempt a conclusion about the most effective regimens considering factors such as reliability of protection, safety and acceptability. We will consider the results of all three studies.

### Reduction in incidence

The risk of a breast-fed or any newborn developing VKDB was significantly lower during the VKDB-02 survey than previously, for two likely reasons. First, there was a steady decline in the proportion of infants not offered VK prophylaxis: during VKDB-90 about 14% of all infants were not offered it, in VKDB-94 about 3% and in VKDB-02, 0% of breast-fed infants.[6] The incidence of VKDB in babies selected (according to assumed risk) to receive no prophylaxis is estimated to be at least 1 in 10 000.[2] Second, there were changes in prophylaxis practice over the period of the three surveys.[6] Between VKDB-90 and VKDB-94 there was a fall in the use of IM prophylaxis and a corresponding increase in oral prophylaxis, both trends reversing by the time of VKDB-02. During VKDB-94 about 60% of babies were routinely offered oral prophylaxis and 25% of these received no doses after day 7, jeopardising protection against late VKDB; by VKDB-02 IM prophylaxis was recommended to 60% and all but three units using oral VK offered the more effective, multiple-dose regimens extending to at least 28 days.

### Parental consent and refusal

Seeking parental consent, either verbal (69%) or written (30%), for VK prophylaxis is now almost universal.[6] In VKDB-94, four of 32 cases had no VK because parents declined it (IM was recommended in one, oral in three). In VKDB-02, four of seven cases had not received prophylaxis because parents declined it; all were born in units where IM prophylaxis was recommended; protocols in three units suggested oral dosing when

**Table 3** Details of babies suffering intracranial haemorrhage (ICH) secondary to VKDB (classified by the criteria of the BPSU studies) in three incidence studies

| Study: | VKDB-90 | VKDB-94 | VKDB-02 |
|---|---|---|---|
| Cases with VKDB | 27 | 32 | 7 |
| Total ICH cases (of which ''probable'')* | 10 (1) | 10 (2) | 0 |
| Deaths from VKDB (of which ''probable'')* | 2 (1) | 0 | 0 |
| Known disability or concern (of which ''probable'')* | 8 | 6 (2) | 0 |
| No adverse outcome | 0 | 3 | 0 |
| Outcome unknown | 0 | 1 | 0 |
| No prophylaxis | 5 | 3 | 0 |
| Single oral dose of VK | 5 | 6 | 0 |
| IM prophylaxis | 0 | 1 (1 mg) | 0 |
| Solely breast fed | 10 | 8† | 0 |
| Liver disease | 4 | 3‡ | 0 |
| Warning bleeds | 7 | 5 | 0 |
| Duration in days, range (median) | 1–14 (6) | 1–4 (2) | – |
| Neither liver disease nor warning bleeds | 1 | 4§ | 0 |

*''probable'', number of cases whose VKDB was ''probable'' rather than confirmed (see text); †soya feeds in two other cases; ‡pancreatic disease in one other; §includes the case with IM prophylaxis and one ''probable'' case.
All instances of death or permanent disability from VKDB are included.

**Table 4** Cases of late VKDB in Great Britain and Ireland†

| Study: | VKDB-90 | VKDB-94 | VKDB-02 |
|---|---|---|---|
| Study duration | 24 months | 24 months | 24 months |
| Birth population | 1 671 000 | 1 609 785 | 1 456 200 |
| a) Idiopathic cases† | 11 | 10 | 0 |
| b) Secondary cases§ | 5 | 13 | 2 |
| c) Predisposing illness¶ | 0 | 1 | 0 |
| Total cases (probables included) | 16 (2) | 24 (3) | 2 |
| Total incidence, a+b+c§§ (95% CI)¶¶ | 0.96 (0.49–1.4)** | 1.5 (0.9–2.1)*** | 0.14 (0.00–0.32) |
| True incidence,†† a+b§§ (95% CI)¶¶ | 0.96 (0.49–1.4)** | 1.4 (0.84–2.0)*** | 0.14 (0.00–0.32) |
| Prophylaxis received | | | |
| Nil | 10 | 6 | 0 |
| Oral×1 | 6 (presumed in 1) | 13 | 0 |
| Oral×2 | Regimen not used | 2 | 1 |
| Oral×3 | Regimen not used | 2 | 1 (probably given) |
| IM | 0 | 1 | 0 |
| Death | 1 | 1 | 0 |
| Handicap (severe) | 8 | 4 or 5 (severe in 3) | 0 |
| Prophylaxis failures (95% CI)¶¶ | | | |
| Complete prophylaxis‡‡ | Data not available | 12 (5–19)* | 2 (0–5) |
| Complete or incomplete | | 16 (8–24)** | 2 (0–5) |
| Unknown | | 8 | – |

*p<0.05, **p<0.01, ***p<0.001, probability of difference from VKDB-02 data.
†Data are from three incidence studies, reclassified as confirmed or probable according to internationally agreed criteria (which are more exclusive than those used in the BPSU reports) to allow comparison with published data from other countries[5]; ‡idiopathic – no cause apparent other than breast feeding; §secondary – predisposing cause found *after* presented with bleeding; ¶"predisposing illness" – illness known to cause VK deficiency diagnosed *before* bleeding, represents failure of targeted prophylaxis or failure of clinical management of cause; ††failure of routine prophylaxis "through inadequacy or omission"; ‡‡received prophylaxis according to policy of birth unit (ie, excludes two babies intended to have none); §§per 100 000 live births; ¶¶assuming a Poisson distribution.

IM was refused so presumably this was also declined. In VKDB-02, refusal was not associated with bleeding in units recommending oral prophylaxis or offering a free choice, so perhaps there is something about the way IM prophylaxis is recommended which invites outright refusal of VK in any form by some parents. This deserves further study; in particular, we would recommend that units sympathetically seek parents' reasons for withholding consent and that those routinely recommending IM prophylaxis review how their alternative oral policy is presented.

### Underlying causes

Liver disease is known to be a major cause of VK deficiency and of late VKDB. That just one case of VKDB was associated with liver disease during VKDB-02 suggests that the various prophylaxis regimens most recently documented do protect even babies with liver disease in the study area, but why should oral prophylaxis be more protective now than previously? Use of multiple doses over 28 days or longer, as discussed above, is one likely factor; another is that, with increased vigilance among parents and professionals, congenital liver disease is recognised earlier than it was previously (P McKiernan, personal communication), allowing appropriate additional VK supplementation and so averting bleeding. In the babies with VKDB and (yet undiagnosed) liver disease, the bilirubin levels were unimpressive at the time of presentation; however, all but two were still jaundiced at 3 weeks of age or more (and presumably had persistently dark urine and pale stools, but these details were not requested).

Predisposing factors other than liver disease were individually rare.

### IM prophylaxis

We are not alone in reporting VKDB after IM prophylaxis (two cases in VKDB-94, one in VKDB-02), but such cases are rare enough that reporting or recording errors must be considered, especially if the bleeding occurs early. The VKDB-02 case met all the diagnostic criteria, was recorded to have received VK 1 mg IM only 2 days previously and suffered no later bleeding; no explanation has been identified.

## IMPLICATIONS

Over the period of these studies, the effectiveness of prophylaxis against VKDB has improved considerably and it is notable that in the latest study parents in four of the seven cases had refused the recommended IM prophylaxis, which almost certainly would have protected; regrettably, the reasons for refusal were not sought. In promoting VK prophylaxis for every newborn baby, we must be as sure as possible that we do no harm to the vast majority who would never bleed without it.

### What is already known on this topic

- VK prophylaxis protects almost all babies if given intramuscularly at birth or by weekly/daily oral doses.
- The reported association between intramuscular VK 1 mg (Cremophor) and increased incidence of leukaemia is unconfirmed, but a small increase in relative risk cannot be excluded.

### What this study adds

- The incidence of VKDB and associated morbidity/mortality fell significantly between 1994 and 2002.
- In 2001–2002 parental refusal of recommended IM injection was the commonest reason for babies with VKDB to have had no VK prophylaxis.
- In babies with VKDB later found to have liver disease, the total bilirubin at the time of bleeding was unimpressive – more important were the proportion of conjugated bilirubin and the fact that most were jaundiced after 3 weeks of age.

There must be some risk associated with any IM injection in a baby (especially in any with an undiagnosed bleeding disorder such as haemophilia) and the reported association between IM VK 1 mg prophylaxis and increased risk of childhood leukaemia is not totally refutable. For these reasons, we remain interested in the possibility of parents giving daily or weekly oral VK drops as a more physiological and acceptable means of routine prophylaxis, as used effectively in some other European countries,[5 9] whilst reserving IM prophylaxis for the minority at highest risk of developing VKDB.

In the UK, Konakion Neonatal (Roche) has now been withdrawn by the manufacturer, in line with its policy for the whole of Europe. The more costly and relatively untried micellar preparation, Konakion MM, must now be used for IM prophylaxis for all high risk babies and for standard risk babies born in units lacking confidence in oral prophylaxis. Monitoring of VKDB has been resumed to document any consequences of the enforced changes in prophylaxis.

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## DEDICATION

The authors wish to pay tribute to the late Professor Dr Anton Sutor, colleague and friend, who did so much to promote understanding of all aspects of vitamin K deficiency bleeding.

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# ARCHIVIST

### Survival after treatment for hyperammonaemic crises of urea cycle disorders

Treatment of urea cycle disorders includes a low-protein diet, adequate calorie intake, alternative-pathway treatment for hyperammonaemic crises, and dialysis if needed. Alternative-pathway treatment consists of giving phenylacetate and benzoate so that waste nitrogen is excreted as phenylacetylglutamine and *N*-benzoylglycine rather than producing ammonia. It was first suggested by Brusilow and colleagues in 1979 and now a multicentre US study extending over 25 years has been reported by researchers including Dr Brusilow (Gregory M Enns and colleagues. *New England Journal of Medicine* 2007;**356**:2282–92; see also editorial, ibid: 2321–2).

The open-label, uncontrolled study, primarily at specialised metabolic diseases centres, included 299 patients with five different enzyme deficiencies: ornithine transcarbamylase deficiency (164 patients; 86 male, 78 female), argininosuccinate synthetase deficiency (80), carbamyl phosphate synthetase deficiency (41), argininosuccinate lyase deficiency (11) and arginase deficiency (3). They were treated during crises with intravenous sodium phenylacetate and sodium benzoate with added arginine hydrochloride in doses appropriate to the specific diagnosis.

In all, 250 (84%) of the children survived. There were 1181 episodes of hyperammonaemia with an episode survival rate of 96%. The survival rate for neonatal crises was 73% and for postneonatal crises it was 98%. Among 93 children over the age of 11 years there were 437 episodes and the episode survival rate was 99%. The likelihood of survival decreased with rising blood ammonium concentrations but nearly all patients with a maximum concentration of 500 μmol/l or less survived. Among patients who were comatose on admission the survival rate was 81%. Among neonates with a maximum blood ammonium concentration >1000 μmol/, the rate of survival was only 38%. Adverse events including cerebral oedema were documented in over half of treated patients. Dialysis was used in 56 neonates and 80 older patients. Overdosage with phenylacetate and benzoate was documented in 13 cases and was fairly frequent during fatal episodes. Clear prescriptions and checking of doses are important and this treatment may be contraindicated in the presence of liver or kidney failure.

These survival rates contrast with neonatal and postneonatal survival rates of 16% and 72% reported in 2005 for patients not given alternative-pathway treatment. More long-term data about neurological outcomes are needed.