Vitamin K Deficiency and Haemorrhagic Disease of the Newborn: A Public Health Problem in Less Developed Countries?

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Vitamin K prophylaxis for newborn infants is widely used in most industrialized countries as well as in hospital settings in many less developed countries (LDCs) in order to prevent haemorrhagic disease of the newborn (HDN). This syndrome mostly affects exclusively breastfed babies. This review is aimed at estimating the magnitude of this problem in LDCs, assessing the need for prophylaxis, its cost-effectiveness and feasibility, and investigating whether current recommendations for breastfeeding promotion should be revised.

Vitamin K is essential for the normal clotting of blood. Newborn infants have low vitamin K levels and HDN may occur within the first 24 hours of life (early HDN), between days 1 and 7 (classic HDN) or from 2-12 weeks (late HDN). The latter is of greatest concern because up to one quarter of affected babies may die from brain haemorrhage and up to one half of the survivors may show permanent neurological disabilities.

Classic and late HDN may be effectively prevented by vitamin K administration soon after birth. Intramuscular vitamin K is highly effective, and oral dosage schemes have also been used in several developed countries. A single oral dose provides partial protection against late HDN but full protection requires multiple doses. Intramuscular vitamin K has rare localized side-effects at the site of the injection. Recently, there has been major concern about the possibility of an association with childhood cancer. Early studies showing such an association, however, have not been confirmed although some degree of controversy remains.

The incidence of late HDN in developed countries ranges from about 4 to about 25 per 100,000 births. No population-based studies are available from less developed countries but there are several reports of this disease, particularly from South and Southeast Asia. The main risk factors for late HDN are gender (males are at a higher risk), warm environmental temperatures and breastfeeding. Breast milk contains low concentrations of this vitamin and the gastrointestinal tracts of breastfed babies are poor in the type of bacteria that help synthesize vitamin K. These infants have up to 20 times greater risk of late HDN than formula fed babies.

Due to the lack of adequate data from LDCs, three incidence scenarios are proposed. Our best estimate is that the warm temperatures and high frequency of breastfeeding will lead to a four-fold increase in incidence relative to industrialized countries. This implies an incidence of 28 per 100,000 births and will be our intermediate incidence scenario. The low incidence scenario assumes that seven out of each 100,000 babies will be affected, corresponding to the median value from developed country studies. The high incidence scenario uses a rate of 72 per 100,000, based on a single hospital-based study from Thailand.

The methodology developed by the World Bank for calculating the loss of DALYs (disability-adjusted life years) was applied to these three scenarios. Late HDN would account for the loss of about one million DALYs among the 126 million children born in 1993, under the intermediate scenario. This represents about 0.23 per cent of all DALYs lost for under-five boys and 0.13 per cent
for girls. The corresponding figures would be 0.06 per cent for boys and 0.03 per cent for girls under the low scenario and 0.59 per cent and 0.34 per cent, respectively, under the high scenario. For the sake of comparison, diarrhoea and pneumonia each account for about 15-20 per cent of all DALYs lost. Comparison of the DALYs lost due to HDN with those due to infectious diseases - against which breastfeeding provides substantial protection - shows that concern with vitamin K deficiency should not be allowed to affect current efforts in breastfeeding promotion.

Based on an estimated cost of US$1.00 per injection, each DALY saved would cost US$133 under the intermediate scenario. This implies a moderate level of cost-effectiveness, inferior to that of most common causes of lost DALYs in childhood. The feasibility of giving vitamin K prophylaxis along with BCG vaccine is discussed.

Vitamin K deficiency fulfills the criteria for constituting a public health problem. Although its incidence is low, its severity and case-fatality are often high. It can be effectively prevented by a relatively safe intervention with moderate cost-effectiveness. Universal recommendations for prophylaxis cannot be made at this stage and decisions must be taken on a national basis. There seem to be three different situations. In the least developed countries, the logistics of delivering vitamin K to newborns would be very complex and there are a number of more cost-effective interventions that are required due to the high burden of disease. In middle-income countries, most births already occur in a hospital and the burden of disease is lower, so that prophylaxis is probably recommended. In industrialized countries, there are strong reasons for supporting universal prophylaxis.

There are many research gaps regarding vitamin K deficiency. Surveys are urgently required for estimating the incidence of HDN from hospital data as well as using biochemical markers of deficiency. Research is also needed to assess the effectiveness of maternal supplementation as a means of preventing disease in the newborn.
Précis

Des mesures prophylactiques comportant l'administration de vitamine K aux nouveau-nés sont couramment prises dans la plupart des pays industrialisés ainsi que dans les hôpitaux de nombreux pays les moins avancés (PMA) pour prévenir l'hémorragie des nouveau-nés. Ce syndrome affecte essentiellement les enfants allaités exclusivement au sein. La présente analyse vise à estimer l'ampleur de ce problème dans les PMA, à évaluer la nécessité des mesures prophylactiques, leur rentabilité et leur faisabilité et à déterminer si les recommandations actuelles de promotion d'allaitement maternel doivent être révisées.

La vitamine K est essentielle à une coagulation normale du sang. Les nouveau-nés ont de faibles taux de vitamine K et l'hémorragie des nouveau-nés peut se produire au cours des 24 premières heures de la vie (hémorragie précoce), entre le 1er et le 7e jour (hémorragie classique) ou entre la 2e et la 12e semaine (hémorragie tardive). C'est cette dernière qui est la plus préoccupante car un quart des nourrissons affectés peuvent mourir d'une hémorragie cérébrale et la moitié de ceux qui survivent risquent d'avoir des lésions neurologiques permanentes.

L'hémorragie classique et tardive des nouveau-nés peut être efficacement prévenue par l'administration de vitamine K peu après la naissance. L'injection intramusculaire de vitamine K est extrêmement efficace et des programmes d'administration par voie buccale ont été également exécutés dans plusieurs pays développés : une seule dose protège partiellement contre l'hémorragie tardive des nouveau-nés mais une protection complète exige l'administration de doses multiples. L'injection intramusculaire de vitamine K comporte des effets secondaires rares, localisés au site de l'injection. Récemment, de vives inquiétudes ont été exprimées concernant la possibilité d'un lien entre la vitamine K et le cancer des enfants. Bien que les premières études indiquant une telle corrélation n'aient pas été confirmées, cette question demeure controversée.

L'incidence de l'hémorragie tardive des nouveau-nés dans les pays développés est d'environ quatre à 25 pour 100 000 naissances. Des études démographiques sur les pays moins développés ne sont pas disponibles mais plusieurs cas ont été signalés, en particulier en Asie du Sud et en Asie du Sud-Est. Les principaux facteurs de risque d'hémorragie tardive des nouveau-nés sont le sexe (les garçons courant un risque plus grand), une température ambiante élevée et l'allaitement maternel. Le lait maternel contient de faibles concentrations de vitamine K et le tube digestif des nourrissons allaités au sein ne contient qu'un petit nombre des bactéries qui aident à synthétiser la vitamine K. Le risque d'hémorragie tardive est 20 fois plus grand pour ces nourrissons que pour les bébés allaités au biberon.

En raison de l'insuffisance de données adéquates sur les PMA, trois scénarios sont proposés. D'après les meilleures estimations disponibles, une température élevée et une grande fréquence de l'allaitement maternel conduiront à une multiplication par quatre de l'incidence de l'hémorragie des nouveau-nés par rapport aux pays industrialisés, soit une incidence de 28 pour 100 000 naissances; c'est le scénario intermédiaire. Le scénario de l'incidence faible prend pour hypothèse une incidence de 7 sur 100 000, ce qui correspond à la valeur médiane dans les pays développés. Le scénario de
l'incidence élevée donne un taux de 72 pour 100 000, chiffre reposant sur une seule étude effectuée dans un hôpital en Thaïlande.

La méthode élaborée par la Banque mondiale pour calculer la perte de DALY (années de vie ajustées pour tenir compte des handicaps) a été appliquée à ces trois scénarios. L'hémorragie tardive des nouveau-nés provoquera la perte d'environ un million de DALY parmi les 126 millions d'enfants nés en 1993 si l'on retient le scénario intermédiaire, soit environ 0,23 % de DALY perdues pour les garçons de moins de 5 ans et 0,13 % pour les filles. Les pourcentages correspondants seraient 0,06 % pour les garçons et 0,03 % pour les filles dans le scénario de l'incidence faible, et 0,59 % et 0,34 % respectivement dans le scénario de l'incidence élevée. A titre de comparaison, la diarrhée et la pneumonie causent environ 15 à 20 % de DALY perdues. Il ressort de la comparaison entre la perte de DALY due à l'hémorragie des nouveau-nés et celle due aux maladies infectieuses (contre lesquelles l'allaitement maternel apporte une protection importante) que les préoccupations sur l'avitaminose K ne doivent pas affecter les activités actuelles de promotion de l'allaitement maternel.

Compte tenu d'un coût estimatif de 1 dollar par injection, chaque DALY gagnée coûtera 133 dollars dans le scénario intermédiaire, ce qui indique une rentabilité modérée, inférieure à celle des interventions menées pour traiter les causes les plus courantes de DALY perdues pendant l'enfance. La possibilité de l'administration prophylactique de la vitamine K conjointement avec le vaccin BCG est à l'examen.

L'avitaminose K satisfait aux critères qui font de ce syndrome un problème de santé publique. Bien que son incidence soit faible, sa gravité et sa létalité sont souvent importantes. L'avitaminose K peut être efficacement prévenue par une intervention relativement sans danger, d'une rentabilité modérée. Des mesures prophylactiques généralisées ne peuvent être recommandées à ce stade, et les décisions doivent être prises au niveau des pays. Il y a, semble-t-il, trois situations différentes. Dans les pays les moins avancés, l'administration de vitamine K aux nouveau-nés se heurtera à des problèmes logistiques d'une extrême complexité, et un certain nombre d'interventions plus rentables seront nécessaires en raison du fardeau écrasant que représente la maladie. Dans les pays à revenu moyen, la plupart des naissances ont déjà lieu en milieu hospitalier et le fardeau de la maladie est moins lourd de sorte que des mesures prophylactiques peuvent probablement être recommandées. Dans les pays industrialisés, il y a de fortes raisons militant en faveur de mesures prophylactiques généralisées.

Il existe de nombreuses lacunes dans les recherches sur l'avitaminose K. Des études sont nécessaires de toute urgence pour estimer l'incidence de l'hémorragie des nouveau-nés à partir des données recueillies dans les hôpitaux ainsi que de l'utilisation des marqueurs biochimiques de l'avitaminose. Des recherches sont également nécessaires pour évaluer l'efficacité de l'administration de suppléments aux mères pour prévenir cette maladie parmi les nouveau-nés.
Síntesis de acción

El empleo de la profilaxis de los recién nacidos con vitamina K está muy difundido en la mayoría de los países industrializados así como en los hospitales de muchos países menos adelantados (PMA) para evitar la enfermedad hemorrágica del recién nacido (EHRN). Este síndrome afecta más que nada a los lactantes alimentados exclusivamente con leche materna. El objeto de este estudio es estimar la magnitud de este problema en los PMA, evaluar la necesidad de dar profilaxis, su efectividad en función de los costos y su factibilidad, e investigar si se deben examinar las recomendaciones actuales para la promoción de la lactancia materna.

La vitamina K es esencial para la coagulación de la sangre. Los recién nacidos tienen niveles bajos de vitamina K y la EHRN se puede presentar en las primeras 24 horas de vida (EHRN precoz), entre los días 1 y 7 (EHRN clásica) y entre la segunda y la doceava semana (EHRN tardía). Esta última es la más grave, puesto que hasta la cuarta parte de los lactantes afectados pueden morir de hemorragia cerebral y hasta la mitad de los sobrevivientes pueden exhibir discapacidades neurológicas permanentes.

Se puede impedir efectivamente la EHRN clásica y tardía administrando vitamina K poco después del nacimiento. La vitamina K intramuscular es sumamente efectiva y en varios países desarrollados se han utilizado también programas de dosificación oral. Una sola dosis oral da protección parcial contra la EHRN tardía, pero para dar protección total se necesitan varias dosis. La vitamina K intramuscular tiene en raras ocasiones efectos secundarios localizados en el sitio de la inyección. Recientemente se ha expresado mucha preocupación acerca de la posibilidad de que la terapia esté asociada con el cáncer infantil. Sin embargo, los primeros estudios que señalan la posibilidad de esta asociación no se han confirmado, aunque la polémica aún existe hasta cierto punto.

La incidencia de EHRN tardía en los países desarrollados se sitúa entre alrededor de 4 y alrededor de 25 por 100,000 nacimientos. En los países menos adelantados no se han llevado estudios basados en la demografía pero hay varios informes sobre esta enfermedad, realizados particularmente en el Sur y el Sureste de Asia. Los principales factores de riesgo de contraer EHRN son el sexo (los varones corren un riesgo más alto), la temperatura cálida del medio ambiente y la lactancia materna. La leche materna contiene concentraciones bajas de esta vitamina y los aparatos gastrointestinales de los lactantes alimentados con leche materna no contienen grandes cantidades del tipo de bacteria que ayuda a sintetizar la vitamina K. Estos niños corren un riesgo hasta 20 veces más alto de contraer EHRN tardía que los lactantes que reciben fórmula alimentaria.

Debido a la falta de datos adecuados sobre la situación en los PMA, se proponen tres hipótesis acerca de su incidencia. Nuestra estimación más exacta es que las temperaturas cálidas y la alta frecuencia de la lactancia materna conducirá a un aumento de cuatro veces de la incidencia en comparación con los países industrializados. Esto presupone una incidencia de 28 por 100,000 nacimientos y será nuestra hipótesis intermedia sobre la incidencia. La hipótesis de incidencia baja supone que siete de cada 100,000 lactantes se verán afectados, lo cual corresponde al valor medio obtenido en los estudios realizados en países desarrollados. La hipótesis de incidencia alta utiliza una
tasa de 72 por 100,000 y se basa en un solo estudio llevado a cabo en un hospital en Tailandia.

La metodología creada por el Banco Mundial para calcular la pérdida de AVADs (años de vida ajustados en función de las discapacidades) se aplicó a estas tres hipótesis. La EHRN tardía causaría la pérdida de alrededor de un millón de AVADs entre los 126 millones de niños nacidos en 1993, si se aplica la hipótesis intermedia. Esto representa alrededor del 0,23 por ciento de todos los AVADs perdidos entre niños varones de menos de cinco años y del 0,13 por ciento en el caso de las niñas. Las cifras correspondientes serían el 0,06 por ciento en el caso de los varones y el 0,03 por ciento en el caso de las niñas si se emplea la hipótesis baja. Con fines de comparación, la diarrea y la neumonía causan alrededor del 15 al 20 por ciento de todos los AVADs perdidos. La comparación de los AVADs perdidos debido a la EHRN con los correspondientes a las enfermedades infecciosas - contra las cuales la lactancia materna ofrece una protección sensible - muestra que no se debe permitir que la deficiencia de vitamina K afecte los esfuerzos que se están llevando a cabo por promover la lactancia materna.

Sobre la base de un precio estimado de un dólar de los Estados Unidos (US$1,00) por inyección, cada AVAD salvado representaría US$133 en el caso de la hipótesis intermedia. Esto significa un nivel moderado de efectividad en función de los costos, inferior al de la mayoría de las causas de pérdida de AVADs en la niñez. Se examina la posibilidad de administrar la profilaxia conjuntamente con la vacuna BCG.

La deficiencia de vitamina K se ajusta a los criterios para que esta situación constituya un problema de salud pública. Aunque su incidencia es baja, su severidad y la mortalidad de los casos son a menudo altas. Puede impedirse efectivamente mediante una intervención relativamente inocua, cuya efectividad en función de los costos es moderada. En estos momentos no se pueden hacer recomendaciones universales sobre la profilaxia y las decisiones se deben adoptar a nivel nacional. Parece haber tres situaciones distintas. En los países menos adelantados, la logística de suministrar vitamina K a los recién nacidos sería muy compleja y hay varias intervenciones más efectivas en función de los gastos que se necesitan debido a la elevada carga patológica. En los países de ingresos medios, la mayoría de los nacimientos ya ocurren en hospitales y la carga patológica es más baja, así que es probable que se recomiende la profilaxia. En los países industrializados, hay razones de peso para apoyar la profilaxia universal.

Hay muchas lagunas en la investigación relativa a la deficiencia de vitamina K. Se necesita llevar a cabo urgentemente encuestas para estimar la incidencia de la EHRN basadas en datos obtenidos de los hospitales y el empleo de marcadores bioquímicos de la deficiencia. También es necesario investigar la efectividad de los suplementos maternos como medio para impedir la enfermedad en el recién nacido.
Introduction

Vitamin K prophylaxis for newborn infants is widely used in most industrialized countries as well as in hospital settings in many less developed countries (LDCs) in order to prevent haemorrhagic disease of the newborn. In addition, a number of studies clearly establish that exclusive breastfeeding markedly increases the incidence of this life-threatening disease. Nevertheless, international organizations have yet to produce guidelines on whether vitamin K prophylaxis is desirable and cost effective, and whether the association with breastfeeding should be reason for concern at a time when its promotion is a major child survival goal.

This review is aimed at filling this information gap. Its objectives include:

a) To estimate the magnitude of vitamin K deficiency and its consequences, among infants from less developed countries.

b) To examine the role of exclusive breastfeeding in vitamin K deficiency and to assess whether breastfeeding promotion strategies should be modified accordingly.

c) To establish whether there is a need for vitamin K prophylaxis in less developed countries.

d) To discuss cost and feasibility issues associated with proposing universal vitamin K supplementation.

Overview

A number of review articles 1,2,3,4,5,6 provide useful overviews of vitamin K and its importance to human beings. Bleeding disorders in newly born infants were first described over 100 years ago when Townsend 7 reported 50 cases in 1894. Vitamin K, however, was only discussed about 40 years later, by Dam, in a study of bleeding disorder in chickens. In a few years following Dam's discovery, several studies reported on the efficacy of vitamin K in the prevention and treatment of newborn bleeding syndromes.

Two different types of this fat-soluble vitamin are found in nature: vitamin K1 occurs in some plants while vitamin K2 is synthesized by bacteria. E. coli bacteria, normally present in the human gut, produce sufficient amounts of vitamin K2 so that normal persons (with the exception of newborns) do not require dietary sources for this vitamin. A third, synthetic substance, vitamin K3, has been available since the 1940s.

Vitamin K is necessary for the synthesis of prothrombin, a blood clotting factor, in the human liver. It also regulates the formation of other clotting factors. Vitamin K deficiency increases the time required for coagulation and may lead to spontaneous bleeding anywhere in the body.

Newborn babies have sterile gastrointestinal tracts and are also likely to be fed on relatively
bacteria-free diets such as breast milk and sterilized cow's milk. In the first weeks of life they are likely to have vitamin K deficiency with resulting low prothrombin levels. This may lead to haemorrhagic disease of the newborn (HDN), which may be characterized as three different clinical patterns (1) - early, classic and late HDN - as shown in Table 1.

Table 1. Clinical types of haemorrhagic disease of the newborn. Adapted from Lane and Hathaway (1).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age</th>
<th>Common bleeding sites</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early HDN</td>
<td>0 to 24 hours</td>
<td>Cephalhaematoma</td>
<td>Maternal drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalp monitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracranial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intrathoracic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intra-abdominal</td>
<td></td>
</tr>
<tr>
<td>Classic HDN</td>
<td>1 to 7 days</td>
<td>Gastrointestinal</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin</td>
<td>Maternal drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circumcision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Umbilicus</td>
<td></td>
</tr>
<tr>
<td>Late HDN</td>
<td>1 to 12 months (2-12 weeks)*</td>
<td>Intracranial</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
<td>Malabsorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use of antibiotics</td>
</tr>
</tbody>
</table>

*Suggested by von Kries and Hanawa (5).

Early HDN is limited to children whose mothers received therapeutic drugs during pregnancy, particularly anticonvulsant and anticoagulant treatments. This extremely rare event will no longer be addressed in the present review.

Classic HDN, as mentioned above, was described in 1894 by Townsend. It is more likely to affect exclusively breastfed infants whose gastrointestinal tract contains relatively few vitamin K-producing bacteria. As Table 1 shows, the bleeding most often affects non-vital organs such as the skin and gastrointestinal tract.

Late HDN was only recognized in 1967 *^8,9*. As the classic syndrome, it tends to affect breastfed babies. Other causes of late HDN include malabsorption syndromes (persistent diarrhoea, cholestatic
jaundice, cystic fibrosis, etc.), since the fat soluble vitamin K - despite being present in the intestines - will not be absorbed properly. Prolonged antibiotic treatment may also lead to vitamin K deficiency by reducing intestinal bacteria. As opposed to classic HDN where bleeding is often limited, late HDN is manifested by sudden Central Nervous System bleeding in about half the cases (3). Its consequences, therefore, tend to be severe. In a review of all reported cases up to 1993\textsuperscript{10}, the mean age was 5.6 weeks. Intracranial bleeding was present in 63 per cent of the infants and the case-fatality was 14 per cent of all cases. Forty per cent of the surviving infants had long-term neurological handicaps.
How common is vitamin K deficiency?

As discussed above, classic HDN is often a mild disease with limited bleeding affecting non-vital organs. Cases are often undetected and self-limited. For this reason, there are relatively few studies of its incidence and those available provide widely contrasting figures, ranging from about 4 to 170 per 100,000 births (see Table 2). A recent review concluded that classic HDN ‘can hardly be considered an important public health problem’ (6). Therefore, the emphasis of this paper will be on the much more severe cases of late HDN, to which most epidemiological studies have been addressed. Table 2 shows the results of the main studies. The available nationwide surveys are also summarized below. Before interpreting these results, however, the following caveats must be considered:

- Several studies were carried out in populations where vitamin K supplementation is the rule. With the exception of the British and German studies, no results are available for unsupplemented children.

- All studies are either based in hospitals or in specialized paediatric clinics. Cases that were not routinely diagnosed or not brought to specialized medical services are not included.

- Several of the surveys had low response rates. Although one may attempt to correct mathematically for these, it is not possible to be sure that services that have not responded will have similar disease rates as the respondents.

- In some surveys, hospitals or clinics were requested to provide information on all cases occurring for the past five years. Whether or not the services had records that were sufficiently organized to provide such information is questionable.

All of the above biases would tend to lead to an underestimation of the true incidence of late HDN.

Incidence Studies in Developed Countries

The studies attempting to collect information on the incidence of HDN for large populations included:

Table 2. Summary of studies on the incidence of haemorrhagic disease of the newborn.
<table>
<thead>
<tr>
<th>Reference/Study Years</th>
<th>Population</th>
<th>Vitamin K prophylaxis status of reference group</th>
<th>Incidence per 100,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classic</td>
</tr>
<tr>
<td>von Kries 1940-70</td>
<td>Review of hospital-based studies in developed countries</td>
<td>Not stated</td>
<td>25 to 170</td>
</tr>
<tr>
<td>Task Force (4) 1993</td>
<td>Review of ‘a number of studies from Europe and Asia’.</td>
<td>Supplemented and unsupplemented</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Supplemented</td>
<td>-</td>
<td>1.4 to 6.4</td>
</tr>
<tr>
<td>Population-based studies</td>
<td>All supplemented (80% orally)</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Ekelund (16) 1987-89</td>
<td>Sweden, population-based reporting</td>
<td>All supplemented (80% orally)</td>
<td>-</td>
</tr>
<tr>
<td>McNinch (15) 1988-90</td>
<td>British Isles, paediatrician-based surveillance</td>
<td>Unsupplemented</td>
<td>8.6</td>
</tr>
<tr>
<td>Nakayama (12) 1978-80</td>
<td>Japan, nationwide hospital study</td>
<td>Not stated</td>
<td>-</td>
</tr>
<tr>
<td>Hanawa (13) 1981-85</td>
<td>Japan, large paediatric hospitals survey</td>
<td>Mostly supplemented</td>
<td>-</td>
</tr>
<tr>
<td>Hanawa (14) 1985-88</td>
<td>Japan, large paediatric hospitals survey</td>
<td>Nearly all supplemented</td>
<td>-</td>
</tr>
<tr>
<td>von Kries (17) 1988-89</td>
<td>Germany, paediatric hospitals survey</td>
<td>Unsupplemented</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated from the data in the original paper.

<sup>b</sup> Adjusted for under-reporting.

- Nakayama<sup>12</sup> reported in 1981 the results of the first nationwide Japanese study of late HDN. Since the original papers are in Japanese, it was not possible to obtain details of the study
methods. An incidence of 25 per 100,000 is reported, apparently after correction for under-reporting.

- In the second nationwide Japanese study, Hanawa et al (Japan)\textsuperscript{13} surveyed all hospitals with 200 or more beds for the period 1981-85. Their response rate was 40 per cent. The overall annual incidence of late HDN was 7.2 per 100,000. Correcting for the low response rate, this would increase to about 20 per 100,000. Some degree of under-reporting is still likely since the study was restricted to large hospitals, information was requested on cases occurring for the past five years and infants who received vitamin K prophylaxis were not excluded.

- A third nationwide study was carried out in Japan from 1985 to 1988\textsuperscript{14}. Again, hospitals with 200 or more beds were contacted and the response rate was 59 per cent. A total of 157 cases were reported, showing a 75 per cent decrease in incidence since the first nationwide study.

- In the United Kingdom and Ireland, McNinch and Tripp\textsuperscript{15} used the notification system of the British Paediatric Surveillance Unit to attempt to detect all cases of HDN occurring in a two year period (1988-90). The system's response rate is 90 per cent. An incidence of 8.6 cases per 100,000 was found for unsupplemented babies. Forty-four per cent of these were classic and 56 per cent late episodes.

- In Sweden\textsuperscript{16}, a nationwide study covered all departments providing in- and out-patient paediatric care. From 1987 to 1989, 17 cases of late HDN were identified (rate of 5.1 per 100,000). About 80 per cent of all infants received oral vitamin K at birth and the remainder received it intramuscularly.

- In Germany\textsuperscript{17}, cases of late HDN were reported in a nationwide study during a 15-month period between 1988 and 1989. Cases were identified by a survey of all paediatric hospitals and population denominators by a survey of all obstetric hospitals, with response rates of 85 per cent and 68 per cent, respectively. The estimated incidence rate was 7.1 per 100,000 for unsupplemented infants.

Incidence in population-based studies from developed countries, therefore, have ranged from about 5 to 25 per 100,000, with a median of 7.1. For the reasons discussed above, these incidences are likely to be underestimated.

**Incidence studies in less developed countries**

Reliable data from less developed countries on the incidence of HDN are hard to come by. Most cases are likely to be undetected due to low coverage of health services in many countries and to the fact that the differential diagnosis of late HDN is difficult in the absence of laboratory or diagnostic imaging resources. For example, an infant with sudden intracranial bleeding may present with convulsions or other neurological symptoms that may be attributed to a number of other diseases.
including meningitis or malaria. Many deaths take place at home so that the true impact of late HDN is impossible to be measured directly.

However, some isolated reports confirm that late HDN is present in LDCs. A report from Thailand mentions an incidence of 72 per 100,000\(^{18}\) based on 453 cases reported between 1964 and 1987, but it is unclear what denominator was used. Another report from Thailand suggests that 35 per cent of newborns have biochemical evidence of vitamin K deficiency in cord blood\(^{19}\), a high value if compared to developed countries. Several case-reports on HDN originate in LDCs, particularly from Asia: India\(^{20,21,22}\), Thailand\(^{23}\), Singapore\(^{24,25}\) and Taiwan\(^{26}\). In Viet Nam, an epidemic of 741 HDN cases was reported in 1981, but this was due to the use of talcum powder accidentally contaminated with the anticoagulant warfarin\(^{27}\).

In the absence of population-based studies, one can attempt to extrapolate from the findings of developed countries to have a better understanding of the situation in less-developed countries. For this extrapolation, it is necessary to know more about risk factors for HDN, which is the topic of the next session.
What are the main risk factors for vitamin K deficiency?

Some risk factors for vitamin K deficiency have already been discussed above. These include maternal medication (mainly anticonvulsant and anticoagulant drugs), malabsorption syndromes (persistent diarrhoea, cystic fibrosis, etc.) and liver disease in infants. In addition, the following risk factors were identified in a number of studies:

**Gender:** Studies of late HDN in Japan (13) and Taiwan (26) reported male to female ratios of 2:1. Ratios of 1.7:1 were also reported in a North American study as well as in a second Japanese study of serum markers of vitamin K (29). In Sweden there were no gender differences (16), and neither the British nor the German studies provided gender breakdown (15)(17).

**Seasonality.** In both population-based studies in the British Isles (15) and in Japan (13), incidence of HDN was about 2.5 times higher in the summer months than in the winter. A similar seasonal pattern was also described in Japan for sub-clinical vitamin K deficiency (30).

**Geographical differences.** Some reviewers have noted that most reports on late HDN from outside Europe and North America originate in the Far East (3). This was confirmed in the present review (see preceding section). It was not possible to locate any population-based study from a developing country. In the second nationwide Japanese study, there was a clear geographical gradient with incidence of late HDN being highest in the Southern than in Northern regions (13). This may suggest that regions closer to the tropics would tend to have higher incidences, but further studies are certainly needed.

**Birth order:** Birth order also seems to affect vitamin K deficiency. In a study from Thailand, biochemical markers of deficiency were present in 51 per cent of first-born babies as compared to 28 per cent of those born later (31). A similar effect of birth order was reported from Japan (29).

**Birth weight:** One study found that biochemical markers of vitamin A deficiency were twice as common among ‘small-for-gestational-age’ babies than among those with an appropriate birth weight but most studies seem to have found no relation to birth weight.

**Breastfeeding:** Human milk has very low concentrations of vitamin K, inferior to those in cow's milk and infant formulae (3). In addition, exclusive breastfeeding results in an intestinal flora that is low in *E. coli*, the bacteria responsible for vitamin K production in the gut. In contrast, infant formulas available in developed countries are fortified with vitamin K so that the infants' requirements are fully met.

As early as 1940, there were reports about preventing HDN by administering cow's milk in the first two days of life (33). In the 1960s, these issues were again raised by reports of increased HDN incidence in lower socio-economic groups from developed countries, where breastfeeding was
common (2). An early North American study then showed that breastfed babies who did not receive vitamin K prophylaxis had 15-20 times greater risk of HDN than those who were either bottle-fed or received supplements.

In the recent pooled analysis carried out by Loughnan and McDougall (10), 95 per cent of the infants with late HDN were breastfed. Most of these studies were carried out in developed countries where bottle feeding is very common. If one assumes that half of the infants aged 1-3 months were bottle-fed, the relative risk associated with breastfeeding would be equal to 19.

The recent prospective studies from developed countries confirmed the role of breastfeeding. In the British surveillance study, McNinch and Tripp (15) reported a relative risk of 12.0 (95 per cent CI 3.6-39.8) for breast versus bottle-fed infants. Given this relative risk and that 40 per cent of babies in the age range are reportedly breastfed, the incidence for breastfed babies would be 19.1 per 100,000. To calculate relative risks for the remaining studies, we have assumed that 50 per cent of all babies would be breastfed at the age of interest. In the second nationwide Japanese study (13), 88 per cent of cases of late HDN were breastfed, a relative risk of about 7.0. In the national German study, 13 out of 14 cases were breastfed, the relative risk being 13. In the Swedish series of 17 infants with late HDN in 1987-89 (16), all 14 infants with information on feeding practices were breastfed. Table 3 summarizes the relative risks from these major studies.

Raised awareness about the importance of exclusive breastfeeding in developed countries resulted in changes in maternity hospital practices in recent years, including the withholding of formula feeding. This has resulted in a recurrence of classic HDN in units where vitamin K supplementation had been abandoned (37)(39).

The evidence for an increased risk of late HDN for breastfed infants is therefore overwhelming. The median relative risk from the population-based studies is 12.5. In addition, most reports emphasize that affected children were "fully" or "exclusively" breastfed. The implications of these findings for the laudable efforts towards the promotion of exclusive breastfeeding in the first 4-6 months of life are discussed below.
Table 3. Relative risks of developing late HDN for breastfed compared to non-breastfed infants, estimated from recent studies.

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Type of study</th>
<th>Relative risk</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Isles (15)</td>
<td>Nationwide surveillance</td>
<td>12</td>
<td>Data from the original paper</td>
</tr>
<tr>
<td>Germany (17)</td>
<td>Nationwide hospital survey</td>
<td>13</td>
<td>Assuming 50% of infants in the age range of occurrence of late HDN are breastfed.</td>
</tr>
<tr>
<td>Japan (13)</td>
<td>Nationwide hospital survey</td>
<td>7</td>
<td>Assuming 50% of infants in the age range of occurrence of late HDN are breastfed.</td>
</tr>
<tr>
<td>Sweden (16)</td>
<td>Nationwide hospital and clinic survey</td>
<td>$+\infty$</td>
<td>The relative risk is equal to $+\infty$ since all cases were breastfed.</td>
</tr>
<tr>
<td>Multi-country (10)</td>
<td>Pooled analysis of case-reports</td>
<td>19</td>
<td>Assuming 50% of infants in the age range of occurrence of late HDN are breastfed.</td>
</tr>
</tbody>
</table>
Can vitamin K deficiency be prevented?

As early as 1961, the American Academy of Paediatrics recommended the prophylactic administration of an intramuscular injection of 0.5 to 1 mg of vitamin K₁ to all newborns. However, enthusiasm for vitamin K prophylaxis in early infancy has waxed and waned in the last decades. Particularly in the late 1970s and early 1980s, concern about side effects and costs, as well as a tendency towards more ‘natural’ therapies, resulted in a widespread abandonment of vitamin K use. These concerns were supported by some studies which failed to find evidence of deficiency in small samples of infants (1). Since severe deficiency is expected in only a small proportion of infants, it is not surprising that small studies may not yield any cases. Furthermore, abandonment of prophylaxis was followed by a number of reports documenting the resurgence of classic and late HDN, a finding that once again confirmed the need for effective vitamin K supplementation (2). More recently, in the 1990s, concern again was raised about the possibility of vitamin K supplements causing childhood cancer (see discussion below under Side-Effects). Once more, this resulted in reduced enthusiasm for injectable vitamin K prophylaxis and led to a switch to oral administration in some countries. Yet again, increased incidences of late HDN as a consequence of these changes were reported.

Despite this history of controversies, there is now widespread consensus that vitamin K prevents the development of classic and late HDN, although there remain discussions of the form of vitamin (K₁, K₂ or K₃), the dose, the timing of doses and the route of administration. The current recommendation (2) is that all infants should receive vitamin K within a few hours from birth. Both intramuscular or oral vitamin K seem to protect equally well against classic HDN.

Substantial controversy remains regarding the choice of oral or intramuscular vitamin K for the prevention of late HDN. Most investigations supporting equal efficacy of both formulations were small studies using biochemical markers as the endpoints. The picture emerging from research on actual HDN cases is quite different. Loughnan and McDougall (39), in the pooled analysis of 131 cases, show that while a single parenteral dose is sufficient, a single oral dose does not completely prevent the disease. However, cases are not seen for about four weeks after an oral dose. They recommend that breastfed babies who received an initial oral dose should continue to receive monthly doses up to five months of age. Formula fed infants do not require further doses unless they have complicating illnesses.

Two of the nationwide studies provided information on the relative effectiveness of oral versus intramuscular vitamin K. In Germany (17), the effectiveness of a single intramuscular injection was estimated at 97 per cent and for single oral administration this was 80 per cent. In the British Isles, data presented by McNinch and Tripp (15) estimate the effectiveness of a vitamin K injection at 99 per cent and of an oral dose at 84 per cent. In the latter study, presence of liver disease substantially decreased the protective effect of the oral - but not of the intramuscular - dose. National data from Sweden (16) and from Switzerland also show an advantage of injectable over oral vitamin K.

The best available studies, therefore, show that a single intramuscular dose is superior to a single
oral dose. The more oral doses an infant receives, the longer the protection (42). There remains the possibility that new oral preparations (including the mixed micellar formulation 45 - given in a single (42) or in multiple doses (40) - might result as effective as parenteral prophylaxis but these formulations require further development and testing.

Another issue with potential policy implications is whether administering vitamin K to the mother will protect the infant. Maternal administration shortly before delivery may also be effective but there is still dispute about the recommended timing and dosage (2) 46. Also, prophylaxis aimed at lactating mothers, may significantly increase milk levels of vitamin K 47,48,49 but there are no studies on the protection afforded against HDN. Further research is required before promoting maternal supplementation as a replacement for vitamin K administration to the newborn.
Are there side-effects to vitamin K prophylaxis?

Parenteral vitamin K, like any injection, may produce localized infections or hematomas at the site of administration. These reactions seem to be very rare, however: no cases were reported in a German survey of 420,000 births (6). Toxic manifestations of synthetic vitamin K₃ include jaundice and hemolytic anaemia in premature infants. These reactions are also extremely rare and do not seem to occur with vitamin K₁ (2).

Two reports from Great Britain in the early 1990s received wide publicity for linking vitamin K prophylaxis to childhood cancer. The first was a cohort study of over 16,000 children born during a one-week period in 1970 ⁵⁰, among whom 33 cases of cancer were identified by the age of 10. An unexpected finding was that children who received vitamin K prophylaxis soon after birth had 2.6 times (95 per cent confidence interval: 1.3 to 5.2) the overall risk of developing cancer than children who did not receive it. The same group of British investigators, led by Golding, carried out a second study using a case-control methodology ⁵¹. Of children born in two major Bristol hospitals between 1965 and 1987, 195 were diagnosed with cancer. They were compared with control children born in the same hospital and year. There was a significant effect of intramuscular vitamin K, with a relative risk of 2.0 (95 per cent confidence interval: 1.3 to 3.0), but no effect of oral vitamin K. The excess risk was observed for leukaemia - the most common childhood cancer - but also for other cancers. Both studies were carefully conducted by experienced researchers.

Since there was no effect of oral vitamin K and since most non-supplemented children were being fed with vitamin K enriched formulas, it is unlikely that vitamin K per se was the carcinogen. The increased risk could be due to some other chemical contained in the injection (5). Another hypothesis would be that the increased risk would be due to a sharp increase in vitamin K concentration in the body that occurs with injectable but not with oral preparations.

These reports generated diverse reactions. In Australia, for example, a national committee recommended the abandonment of injectable vitamin K⁵². A German committee recommended no immediate change (5). In the United States, a task force report⁵³ questioned the findings of the Golding studies on the following basis:

- If vitamin K really doubled the incidence of leukaemia, then a major increase should have been observed since 1961 in the US when the Academy of Pediatrics recommended its routine administration. However, there was no such increase. The apparent increase in the United Kingdom suggested by Golding has been strongly disputed ⁵⁴. Also, no increase was observed in Denmark despite universal adoption of vitamin K prophylaxis ⁵⁵.

- There were reported increases in multiple types of cancer. However, it is very unlikely that any agent would affect multiple cancer types. Environmental radiation may be the only exception, but even among children from Hiroshima and Nagasaki there was no generalized increase in childhood cancer.
• The biological plausibility explanation put forward by Golding (induction of sister chromatid exchanges) is questionable since more specific tests are available. Also, the only in vivo study showed no difference in chromatid exchanges between infants who received vitamin K and those who did not.

These arguments were reinforced by von Kries and Hanawa (5), who pointed out that vitamin K injections in the United Kingdom have been traditionally given to infants with perinatal risk factors. If these babies also have a higher cancer risk, a spurious association with vitamin K might be found. Golding et al. controlled for admission to special care units and refuted this argument but it is still possible that some other unidentified factors may be operating.

Evidence from the US also challenges the British findings. There was no increase in childhood leukaemia since vitamin K prophylaxis was introduced 56. A recent reanalysis of the Collaborative Perinatal Project, a multi-centre study of about 55,000 births from 1959 to 1966 57, identified 48 cases of cancer by the age of eight. Vitamin K was associated with a relative risk of 0.84 (95 per cent confidence interval: 0.41 to 1.71), that is, with a small but non-significant reduction in cancer risk.

Further, strong evidence against a carcinogenic role for injectable vitamin K is presented in a Swedish cohort study. All infants born from 1973 to 1989 (totalling over 1.3 million) were studied through their birth records and 2,354 cancer cases were identified in the national cancer registry. There was no increase in cancer incidence in infants receiving intramuscular vitamin K compared to oral prophylaxis (relative risk of 1.01; 95 per cent confidence interval 0.88 to 1.17).

While the British papers raise concern, the weight of the evidence seems to be against an association between vitamin K and cancer. Further studies, however, are required to settle this issue. It has been argued that only randomized controlled trials will solve the controversy 58 but there would be major ethical and logistical difficulties.
What are the national policies and practices regarding vitamin K prophylaxis?

Policies and practices vary markedly from country to country. A review carried out in Europe in 1989 is summarized in Table 4.

Table 4. Practices regarding vitamin K administration to newborns in the late 1980s in European countries (14 respondents).

<table>
<thead>
<tr>
<th>Proportions of newborns receiving vitamin K according to route</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>70-90%</td>
<td>10-30%</td>
</tr>
<tr>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>&quot;Most&quot;</td>
<td>&quot;Few&quot;</td>
</tr>
<tr>
<td>Practices vary widely</td>
<td>France, Netherlands</td>
</tr>
<tr>
<td>High-risk babies only</td>
<td>Poland, Hungary</td>
</tr>
<tr>
<td>University hospitals only</td>
<td>Turkey</td>
</tr>
</tbody>
</table>

National practices therefore vary widely within Europe. In the USA, all newborns receive intramuscular vitamin K since the oral preparations have not been licensed. In addition to variability among countries, national policies often specify different regimens for different children. Table 5 shows three examples. While in the US a universal recommendation is given, both in the Netherlands and in the Czech Republic policies are complex. From the standpoint of less developed countries, simple policies are required. While little or no information is available from these countries, vitamin K tends to be administered only in selected hospitals, such as those linked to universities.
<table>
<thead>
<tr>
<th>Country (Reference)</th>
<th>Target population</th>
<th>Route and dosage</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IM</td>
<td>Oral</td>
</tr>
<tr>
<td>US(36)</td>
<td>All newborns</td>
<td>0.5-1 mg.</td>
<td></td>
</tr>
<tr>
<td>Holland(^{61})</td>
<td>Not at risk</td>
<td>1 mg. at birth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perinatal risk</td>
<td>1 mg.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breastfed</td>
<td>25 (\mu)g daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breastfed, high-risk</td>
<td>50 (\mu)g daily</td>
<td></td>
</tr>
<tr>
<td>Czech Republic(^{62})</td>
<td>Not at risk</td>
<td>1 mg.</td>
<td>1 mg.</td>
</tr>
<tr>
<td></td>
<td>Pre-term, high-risk</td>
<td>1 mg.</td>
<td>1 mg. weekly up to 1 month</td>
</tr>
<tr>
<td></td>
<td>Breastfed</td>
<td></td>
<td>1 mg. monthly up to 6 months</td>
</tr>
</tbody>
</table>

Note: Unless otherwise stated, all dosages refer to vitamin K\(_1\) given at birth.
Is vitamin K deficiency a public health problem deserving intervention in less developed countries?

Reliable studies of the incidence in LDCs are not available. It is therefore necessary to estimate it on the basis of other studies. The nationwide studies from developed countries showed a median incidence of late HDN of 7.1 per 100,000 (range 4.8 to 25). These figures are probably underestimated due to a number of possible biases. In addition, infants from LDCs have a number of risk factors that would tend to lead to higher incidence of late HDN. These include the high frequency of breastfeeding in most countries, the warm temperatures and the higher incidence of persistent diarrhoea, a cause of malabsorption.

In both England and Japan, warm temperatures were associated with at least a doubling of the incidence. This is supported but the major North-to-South gradient observed within Japan. In societies where breastfeeding is universal, incidence rates would also tend to be double those of countries where about 50 per cent of infants are breastfed in the first 2-3 months. The effect of persistent diarrhoea is harder to quantify. However, if one assumes that both breastfeeding and warmer temperatures would each double the incidence, one might conservatively assume that LDCs would have about four times the median incidence observed in developed countries, that is, about 28 per 100,000 births.

This figure will be used as our ‘best estimate’ in the forthcoming estimates of disease impact. Two other scenarios will also be used, one with low and another with high incidence (Table 6).

### Table 6. Three possible scenarios for incidence of late HDN in less developed countries.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Incidence per 100,000</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>7</td>
<td>Median value from studies in developed countries</td>
</tr>
<tr>
<td>Intermediate</td>
<td>28</td>
<td>Above value multiplied by four to account for breastfeeding and warm climate</td>
</tr>
<tr>
<td>High</td>
<td>72</td>
<td>Results from Thai study (18)</td>
</tr>
</tbody>
</table>

Late HDN may cause not only mortality but also lifelong disability. Using a methodology developed by the World Bank, disability-adjusted life years (DALYs) were calculated for estimating the burden of late HDN in less developed countries. Data from a review of all reported cases up to 1993 (10) were used as the basis for estimating the impact on mortality and disability. Intracranial bleeding was present in 63 per cent of the infants and the case-fatality was 14 per cent of all cases. Forty per cent of the surviving infants had long-term neurological handicaps. The Thai study (18) suggested a case-fatality of 22 per cent and the presence of handicaps in ‘25-67 per cent’. Given that both mortality and permanent impairments are likely to be more common in LDCs due to lack of
adequate treatment, we will use a case-fatality of 25 per cent and disability of 50 per cent of the survivors (that it, 37.5 per cent of all infants affected) in the following calculations. Additional assumptions were made for calculating DALYs. The results are presented in Table 7.

Table 7. Number and per cent of DALYs (disability-adjusted life years) lost due to late HDN in less developed countries.

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>Incidence per 100,000</th>
<th>Estimated number of DALYs lost</th>
<th>Per cent*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Both sexes</td>
<td>Boys</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>237,527</td>
<td>154,071</td>
</tr>
<tr>
<td>Intermediate</td>
<td>28</td>
<td>950,107</td>
<td>616,285</td>
</tr>
<tr>
<td>High</td>
<td>72</td>
<td>2,443,131</td>
<td>1,584,734</td>
</tr>
</tbody>
</table>

* Percentage of the estimated total DALYs lost among under-five boys (268 million) and girls (250 millions) in less developed countries.

Table 8 shows the main causes of lost DALYs among under-five children from LDCs (63). Based on the intermediate scenario for late HDN, its impact is considerably smaller than most common childhood diseases. For example, diarrhoea and respiratory infections account each for 15-20 per cent of DALYs lost. Of the vaccine-preventable diseases, measles accounts for 5-6 per cent, neonatal tetanus for about 3 per cent, pertussis for about 2 per cent and polio for 0.3-0.4 per cent. The impact of late HDN would thus be about half that of polio.

* Additional assumptions for DALYs calculation: Further assumptions: boys twice as affected as girls; average age at incidence 6 weeks; disability is lifelong. One half of children with a disability would be graded as Class 3 disability, that is, would have limited ability to perform activities in two or more of the following areas: recreation, education, procreation or occupation. The remaining would have a more severe Class 4 disability, with limited ability in all four above areas.
Table 8.  Percentage of DALYs lost by groups of causes in under-five children from less developed countries, 1990 (World Development Report 1993 (63)).

<table>
<thead>
<tr>
<th>Diseases and injuries</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>All communicable and perinatal conditions</td>
<td>73.2%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>STD/HIV</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>16.2%</td>
<td>15.7%</td>
</tr>
<tr>
<td>Childhood cluster</td>
<td>10.7%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Polio</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Measles</td>
<td>5.6%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>2.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Malaria</td>
<td>4.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>18.5%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Perinatal</td>
<td>17.2%</td>
<td>19.9%</td>
</tr>
<tr>
<td>Noncommunicable</td>
<td>21.1%</td>
<td>19.9%</td>
</tr>
<tr>
<td>Nutritional and endocrine</td>
<td>6.4%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Protein-energy malnutrition</td>
<td>2.4%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>2.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Anaemias</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
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<td>1.0%</td>
</tr>
<tr>
<td>Epilepsy</td>
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<td>0.3%</td>
</tr>
<tr>
<td>Respiratory</td>
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<td>1.8%</td>
</tr>
<tr>
<td>Asthma</td>
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<td>0.2%</td>
</tr>
<tr>
<td>Congenital</td>
<td>6.5%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Injuries</td>
<td>5.7%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Unintentional</td>
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<td>4.6%</td>
</tr>
<tr>
<td>Motor vehicles</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Falls</td>
<td>1.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Drowning</td>
<td>0.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Intentional</td>
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<td>0.8%</td>
</tr>
<tr>
<td>Late haemorrhagic disease of the newborn*</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
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</table>

* Based on the findings of the present review.
How cost-effective and feasible is vitamin K prophylaxis in LDCs?

Two papers discussed issues of cost-effectiveness of vitamin K prophylaxis, both in the context of developed countries. Costs in Germany (6) were estimated at US$1.00 per intramuscular dose (including the vitamin, syringe and needle) and at US$0.06 per oral dose. These do not include the costs of administering the vitamin. In New Zealand (46), the cost of intramuscular prophylaxis was estimated at US$1.13 (presumably including needle and syringe) compared to US$0.34 per oral dose (2 cents for bulk drug and 32 cents for dispensing costs). Both studies concluded that the prophylaxis is cost-effective: the costs for preventing one case are considerably smaller than those of treating the affected infant and looking after survivors with lifelong disabilities. In Germany, the cost for preventing one case of intracranial haemorrhage due to late HDN is estimated at about US$30,000 using injectable vitamin K, which is certainly lower than that of the lifelong costs to society of the handicaps caused by this cost. In New Zealand, using different incidence assumptions, it was estimated that each life saved would cost US$11,000 given a programme with injectable prophylaxis.

Assuming a cost of US$1.00 per injectable dose, our calculations show that saving one DALY would cost US$533 in the low-incidence, US$133 in the intermediate and US$52 in the high-incidence scenarios. The World Bank report (63) classifies as cost-effective interventions those under US$100 per DALY saved, and as moderately cost-effective those costing US$250-999 per DALY. The report notes that there are very few interventions in the range of US$100-250, exactly where our intermediate estimate would lie.

In the assessment of the World Development Report, cost-effective interventions exist against all but two of the ten major causes of lost DALYs for under-fives. The exceptions are congenital malformations (the fifth cause for both genders) and falls (the tenth cause for girls)(63).

Two more issues must be addressed regarding the feasibility of vitamin K prophylaxis in LDCs:

- **Timing.** Prophylaxis must occur soon after birth. To prevent classic HDN, it should be administered in the first two days of life. An early injectable dose will also prevent late HDN - the dose may be given as late as two weeks of age. Where many births occur outside health facilities, vitamin K prophylaxis will present important logistical problems. Possible alternatives include training traditional birth attendants and joint administration with the BCG vaccine.

- **Intramuscular versus oral administration.** As discussed, oral administration is less traumatic, has fewer side effects and is less expensive. However, repeated doses are required with currently existing formulations. This implies major logistical problems for less developed countries, mainly since monthly doses would be necessary in the first 5-6 months of life. A single injectable dose may be given at the same time as the BCG vaccine but two separate injections are required since the vaccine is administered intradermically. This has clear logistical advantages but giving a newborn two simultaneous injections may be poorly accepted by the families. There is no need for a cold chain since vitamin K preparations are stable under ambient temperatures.
These cost and feasibility issues must be addressed in the context of each country.
Is HDN sufficiently common to warrant changes in breastfeeding promotion?

Breastfeeding promotion has been a stronghold of child survival strategies. As discussed above, the concern that breastfeeding increases the risk of HDN is strongly supported by the available data. The information on DALYs lost due to different diseases, however, may be used to assess the wisdom of proposing changes in breastfeeding patterns due to this concern. Non-breastfed infants are 14 times more likely to die due to diarrhoea, four times due to respiratory infections and 2.5 times due to other infections. Together, these conditions account for over half all DALYs lost among under-fives in LDCs (Table 8). No sophisticated calculations are required to show that the 0.1-0.2 per cent of DALYs lost due to late HDN are negligible when compared to the protection afforded by breastfeeding against the major child killers.
Conclusions and recommendations

Our conclusions for deciding whether vitamin K prophylaxis should be recommended, will be based on the criteria recommended by von Kries (6), in the context of industrialized countries. The above-presented data allow us to examine these criteria in relation to LDCs.

- **The disease should be an important problem with respect to its incidence, severity or both.** Although the incidence of late HDN appears to be relatively small in most countries, the disease has a high degree of severity due to its substantial case-fatality and the frequency of lifelong impairment. The answer to this first criterion is therefore positive.

- **The prophylactic measure should be effective in preventing the disease.** There is substantial evidence that injectable vitamin K and probably repeated dosage of oral vitamin K protect against late HDN.

- **The benefits of the prophylactic measure should clearly prevail against potential harmful effects.** The concerns about the carcinogenic role of injectable vitamin K have not been confirmed by recent studies. Although further research is required, it is likely that vitamin K will be acquitted. Other side-effects are rare. The benefits therefore, seem to outweigh the risks.

- **The costs of the prophylactic measures should balance the costs for the treatment of the disease and its long-term sequelae as well as the expenses of other aspects of health care.** The cost of vitamin K prophylaxis are considerably smaller than the economic consequences of the disease. Whether or not a prophylactic programme is recommended will depend on the burden of disease in each country, on the resources available for health care, and on whether cost-effective interventions are available for the most prevalent diseases.

On the basis of these four criteria, it is evident that final decisions on vitamin K will have to be taken on a country-by-country basis. From the standpoint of an international organization such as UNICEF, the following broad recommendations may be made:

- **In the least developed countries**, most deliveries will take place at home - a fact that will complicate the delivery of prophylaxis. In addition, since the burden of infectious diseases in these countries is likely to be high, more cost-effective interventions are available against these conditions than for HDN. Health budgets are also likely to be constrained. Therefore, prophylaxis is unlikely to be recommended for these countries.

- **For middle-income countries** - where most births already take place in hospitals and easily preventable diseases are becoming less common - vitamin K prophylaxis is probably recommended.

- **In industrialized countries**, vitamin K prophylaxis is certainly cost-effective and should be
encouraged.

It should be stressed that the above conclusions and recommendations are made on the basis of very incomplete data. For example, there are no reliable studies of the incidence of vitamin K deficiency or HDN in less developed countries. To better appreciate the magnitude of this problem and of possible solutions, the following lines of research are recommended.

- **Prevalence studies of vitamin K deficiency through biochemical markers.** The accurate assessment of deficiency through these markers, including PIVKA (protein induced by vitamin K absence), require sample sizes that are many times smaller than those demanded by studies of actual HDN.

- **Hospital based surveys of HDN.** Virtually all of the information on HDN in developed countries comes from retrospective studies of hospital records. Although in LDCs many births occur at home and the quality of hospital records may be poor, these studies would be inexpensive and might provide at least an approximation of the actual magnitude of the problem.

- **Effectiveness of maternal prophylaxis.** Research is needed on the comparison of maternal and infant prophylaxis, particularly in contexts were breastfeeding is highly prevalent. Maternal supplementation may solve several of the problems faced with infant prophylaxis, including the need for supplementation immediately after birth, the inconvenience of intramuscular injections in the newborn and the unconfirmed association with childhood cancer.
End-notes


