Vitamin K supplementation to prevent hemorrhagic morbidity and mortality of newborns in India and China

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Background: **Vitamin K deficiency bleeding (VKDB) can cause prolonged and bleeding (intracranial hemorrhage) among newborns, which can be life-threatening or lead to long-term morbidity. The aim of this review article is to reiterate empirical evidence to support the argument that vitamin K should be mandatory for newborns in India and China, as well as in other countries with a high burden of neonatal deaths.**

Data sources: **Studies were integrated from the PubMed/MEDLINE database search, as well as related literature available elsewhere.**

Results: **Both India and China have been slow in adopting an effective program for administering vitamin K injections to newborns to prevent VKDB-related morbidity and mortality. VKDB cases in China and India have shown inadequate attention to routine use of vitamin K by injection.**

Conclusions: **While no reliable data are publicly available, the issue of VKDB is at last receiving some attention from the Chinese public health system as well as the Indian government. In both countries, routine vitamin K administration to newborns would prove to be a cost-effective intervention to reduce preventable neonatal morbidity and mortality. VKDB is a global neonatal care issue, including countries where parental resistance is preventing babies from defense against this life-threatening condition.**

World J Pediatr 2017;13(1):15-19

Key words: **global health;**
hemorrhagic disease of the newborn;
intracranial hemorrhage;
neonatal mortality;
vitamin K deficiency bleeding disorder

Review article

Vitamin K deficiency bleeding (VKDB) (previously known as hemorrhagic disease of the newborn or HDN) is of particular concern in neonates as they are born with low levels of vitamin K. The risk of morbidity and mortality from hemorrhage increases among newborns who do not receive vitamin K prophylaxis at birth. VKDB can cause prolonged and excessive bleeding, including intracranial hemorrhage (ICH) which is life-threatening and may even lead to long-term morbidity. Vitamin K deficiency as a cause of HDN has long been a known clinical entity, and its relationship with HDN was discovered by Danish biochemist Henrik Dam in 1939 along with American researcher Edward Doisy, for which they were awarded the 1943 Nobel Prize in physiology or medicine for their discovery of vitamin K and its chemical nature.[1]

VKDB can occur as one of three distinct presentations: early, classical or late. Early disease occurs in the first 24 hours of life and is often associated with *in utero* exposure to anticonvulsant or anticoagulant medications. The bleeding associated with early onset of the disease is usually serious with intracranial bleeding being common. The classical disease is usually seen from one to seven days, primarily in breastfed infants who did not receive vitamin K prophylaxis at birth. Late-onset VKDB is seen in infants older than one week of age and up to several months. It is often associated with exclusive breast-feeding. Late onset VKDB typically presents a gastrointestinal, cutaneous or intracranial hemorrhage.[2]

Reliable global statistics on the incidence of early and classical VKDB are not available.[3] Some comparisons in incidence of late VKDB data among countries have been published from nationally representative surveillance programs in the UK, the Netherlands, Germany, Switzerland, Australia, New Zealand, Thailand, China,

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doi: 10.1007/s12519-016-0062-6
Online First, November 2016

Vietnam, and Japan.[4] The incidence of late VKDB in infants not receiving vitamin K prophylaxis has been shown to be $5/10^5$ births in Western European countries compared to 11 and 72 per 10^5 births in Japan and Thailand, respectively.[4] Altogether, the nationwide estimates from developed countries show a median incidence of late VKDB of $7.1/10^5$ (range $4.8/10^5$ to $25/10^5$), however these figures are probably underestimated due to a number of possible biases of under-reporting and masking by other morbid conditions.[5]

Vitamin K prophylaxis in newborns: evidence

The need for vitamin K prophylaxis to avoid VKDB among newborns is well established. Since 1961, the American Academy of Pediatrics (AAP) has recommended vitamin K by injection for all newborns, and this procedure was made mandatory in most states with the virtual disappearance of VKDB as a cause of death in the US, and reaffirmed by the AAP in 2003.[6] Vitamin K by injection within 6 hours of birth was made mandatory in New York State in 1988,[7] and subsequently in all states of the United States, and many other countries, including Australia, Canada, Denmark, Germany, Israel, and the Netherlands. However, a recent incident of four cases of VKDB in Tennessee in the US was attributed to parental refusal to accept vitamin K injections. Of the four cases, one child died, while others suffered varying degrees of brain damage.[8] As part of the ensuing investigation in Tennessee by the Centers for Disease Control (CDC), Schulte and colleagues from the Vanderbilt University Medical Center reported in seven infants with confirmed vitamin K deficiency, of whom five developed VKDB.[9] In December 2014, a similar incident made headlines of an Israeli daily news (Jerusalem Post), where a one-month old girl had to undergo surgery due to ICH because of parental refusal of a vitamin K injection.[10] The phenomenon of a return of VKBD can be attributed to refusals by parents, along with refusal of vaccinations, due to lack of awareness that vitamin K is a safe measure for newborns to prevent serious bleeding.[11]

Before and after the 1961 AAP recommendation of intramuscular (IM) prophylaxis for all newborns in the United States, vitamin K has been used widely for decades and shown to be safe and effective at preventing early, classical, and late VKDB. However, some countries chose an oral prophylaxis regimen following a 1990 peer-reviewed British study (with no prior hypothesis) claimed that IM prophylactic vitamin K could be associated with a risk of childhood cancer.[12] Further studies carried out by the working group of WHO International Agency for Research on Cancer (IARC),[13] and two independent studies[14,15] showed no evidence to support this alleged association. Thus, the false claim of IM being a risk factor for childhood cancer was followed by re-confirmation that IM- administered vitamin K is the safest and most cost-effective way.[16]

Nevertheless, internationally, the doubt and concern of cancer risk lingers in public consciousness such that method of administration varies and is still under debate, with oral administration recommended in some countries, or the decision left to the individual physician's judgment.[16-18] In a UK survey of maternity units, 60% recommended IM prophylaxis and 25% recommended oral prophylaxis, the remainder made no recommendation about the method.[18] One of the reasons for such heterogeneity could be attributed to the several forms of vitamins K prophylaxis (vitamin K_1 or phylloquinone, vitamin K_2 or menaquinone, and vitamin K_3 or menadione) becoming available.[17]

A Cochrane review[19] in 2000 of prophylactic vitamin K for prevention of intraventricular hemorrhage concluded that a single dose (1.0 mg) of IM vitamin K after birth is effective in the prevention of classic HDN, and IM or oral (1.0 mg) vitamin K prophylaxis improves biochemical indices of coagulation status at 1 to 7 days. However, oral vitamin K, which requires multiple doses, has shown inconclusive results in prevention of late HDN. Studies that used biochemical indicators of effectiveness cannot be correlated with the actual coagulation status of the newborn due to lack of scientific evidence.[17] Another Cochrane review in 2001[20] on vitamin K administration to pregnant women before preterm delivery concluded that antenatal vitamin K was associated with a non-significant trend toward reducing all grades of periventricular hemorrhage.

Despite reliable evidence on the effectiveness and safety of vitamin K injections, international public health organizations, leaders, and policy makers engaged in work to reduce neonatal mortality are not proactive in advocating vitamin K for newborns globally. For example, the 2005 *Lancet*'s series on "Newborn Survival"[21] failed to include the problem of VKDB among newborns, though almost 10 years later the VKDB received some attention in the 2014 "Every Newborn"[22] series published in the same journal.

We want to reiterate empirical evidence to support the argument that vitamin K should be mandatory for newborns in India and China, as well as in other countries with a high burden of neonatal deaths.

Vitamin K prophylaxis in India and China: policy and practice

Both India and China have been slow in adopting an effective program for administering vitamin K

injections to newborns to prevent VKDB-related morbidity and mortality. India and China together account for almost 37% of the world's population and thus are crucial for attaining Millennium Development Goal 4 (MDG 4) - to reduce two thirds of the under-five mortality rate (U5MR) between 1990 and 2015. According to 2014 UN estimates, India's U5MR declined from 126 per 1000 live births in 1990 to 53 per 1000 live births in 2013 as compared to the target of 42 per 1000 live births by 2015.[23] In the same period, China achieved the MDG target with a 2013 U5MR of 13 per 1000 live births.[23] Neonatal deaths, however, remain a daunting challenge in both India and China, accounting for 61% and 55% of China and India's under-five deaths, respectively.[24] In India, about 760 000 neonates die every year, a neonatal mortality rate (NMR) of 29 per 1000 live births, while the NMR of China is 8 per 1000 live births.[23]

After a long delay, in 2014 India's Ministry of Health and Family Welfare (MoHFW) introduced mandatory routine vitamin K injections for newborns at birth in health facilities at all levels including the sub-centers, the lowest level of public healthcare facility.[25,26] The operational guidelines of vitamin K administration issued by the MoHFW admits that reliable estimates of VKDB in India are not available, but accepts that there is agreement among experts that prevention of neonatal death in India will require implementation of vitamin K as routine IM administration at birth. For example, in a follow up study (from January 1998 to December 2001) of 42 infants diagnosed with VKDB who had not received vitamin K in India, 71% suffered intracranial hemorrhage.[27] Although a poorly designed hospital based study, it still offers some insights to the problem of VKDB in India. It is worth mentioning that although India has delayed adoption of vitamin K, a landmark study in rural India[28] conducted in 1999 had established that administering vitamin K at home by trained community health workers can substantially reduce overall neonatal morbidity and mortality. Indian MoHFW guidelines issued in 2014 recommended that "all newborns delivered in health facilities at all levels including a sub-center should receive vitamin K prophylaxis", and "vitamin K prophylaxis is given as a single dose IM injection soon after birth".[25]

In China, the 2007 Dietary Guidelines for Chinese Residents (an update from the 1997 version) released jointly by the Ministry of Health and Chinese Nutrition Society recommended vitamin K by injection or oral administration to every newborn and infant under six months.[29] The Ministry of Health Policy on vitamin K is a well developed entity and committed to reduceing the level of VKDB in China. In contrast to India where data are not available, regional surveys in China have yielded valuable incidence data on VKDB. However for national as well as international comparisons, comparing incidence data is problematic because of different methodologies and case definitions. A study[30] conducted in 1999 indicated that among 31 649 neonates in seven provinces, VKDB morbidity was 2.4% with a case fatality rate of nearly 30.3%. This same study concluded that the incidence of late VKDB of newborns ranges from 0.04% to 0.69%. In addition, a 2004 Chinese study with 3970 cases presented an ICH rate of 92%, with a case fatality rate of 22%.[31] All these studies concluded that VKDB was a commonly fatal disease to neonates in China and that vitamin K supplementation should be promoted along with breastfeeding. A review of epidemiological studies on the incidence of late VKDB indicated that China has a higher rate of VKDB than India,[4] although no data were available supporting this statement. Both India and China have a number of risk factors those tend to lead to a higher incidence of late HDN. These include low birth weight, the high frequency of breastfeeding, warmer temperatures, and the higher incidence of persistent diarrhea, a cause of malabsorption.[5]

Administration of vitamin K in China varies by hospital departments, geographic areas and dosage. A 2003 study[32] in China reported that of 126 sampled hospitals, only 72 gave routine vitamin K_1 to every newborn. The provincial hospitals have the highest rate of vitamin K usage (29/44, 65.9%); the municipal level hospitals have the second highest rate (38/68, 55.9%); hospitals at the village level have the lowest rate (5/14, 38.5%). While hospitals in developed countries have reached consensus and widely applied the preventative procedure. Chinese scholars reported that it was still a controversial issue in the country, so the practice was not optimal. Implementation of vitamin K prophylaxis to deal with VKDB in Hong Kong of China was introduced in 1993 with both IM and oral administration recommended. Although there has not been a systematic report published detailing the progress in Hong Kong of China, the study reported no single case of VKDB since the adoption of prophylaxis for every newborn for six years up to 2003.[33]

As indicated above, reliable studies of the incidence of VKDB in India and China are not available. To verify the availability of the literature on VKDB in India and China, a systematic review using the PubMed/MEDLINE database was conducted. As of April 1, 2015, a total of 28 studies on varying manifestations of vitamin K deficiency were indentified on India, whereas 20 studies on China were recorded in PubMed/MEDLINE. However, a total of six studies (five on India, and one on China) focusing on reporting VKDB or HDN cases or research are represented in Table

Table. Selected studies available on vitamin K deficiency bleeding (VKDB), or hemorrhagic disease of the newborn (HDN) in India and China on PubMed/MEDLINE, as on April 1, 2015

Leading author (PubMed ID)	Year of publication	Journals	Type of study	Cases	Early/Classical/ Late	Clinical presentations
Gahalaut P (PMID: 24082204)	2013	Indian Journal of Dermatology	Case report	1	8 mon	Nodular purpura
Gopakumar H (PMID: 21042512)	2010	Journal of Pediatric Neurosciences	Case report	1	2 mon	Intracranial hemorrhage
Pooni PA (PMID: 12657759)	2003	Indian Pediatrics	Clinical profile	30	Late	Intracranial hemorrhage
D'Souza IE (PMID: 12657755)	2003	Indian Pediatrics	Clinical profile	14	Late	Intracranial hemorrhage
Merchant RH (PMID: 2583806)	1989	Indian Pediatrics	Case report	9	3 wk to 7 mon	Acute intracranial hemorrhage
Zhou F (PMID: 12411188)	2002	Zhonghua Yu Fang Yi Xue Za Zhi	Matched case-control study	3.27/ 1000	<6 mon	Vitamin K deficiency bleeding

Review article

1. The paucity of studies available, especially in the English language in PubMed/MEDLINE, is indicative of a serious dearth of reliable data on VKDB in India and China which requires urgent attention.

A review of the cost implications of vitamin K administered intramuscularly indicates that saving one disability-adjusted life year (DALY) would cost $533 in the 'low', $133 in the 'intermediate' and $52 in the 'high' incidence scenario.[34] Based on the World Bank 1998 classification of interventions costing under $100 as 'cost-effective' while those costing between $250-999 per DALY as 'moderately cost-effective', vitamin K prophylaxis can be said to be cost effective only in the high incidence scenarios.[34] In addition, a 2004 study in Hanoi indicated that routine vitamin K prophylaxis would significantly reduce infant morbidity and mortality in Vietnam and cost an estimated US$87 per DALY saved, thus proving a highly cost effective intervention.[35]

In many Asian developing countries, most deliveries still take place at home,[36] complicating safe delivery and prophylaxis.[37] In countries with a high burden of neonatal mortality, action to prevent VKDB should be given a high priority with proper budgetary allocation. Failure to address this issue will significantly hamper efforts to further reduce child, especially neonatal, mortality as is already apparent in many countries which will not attain MDG 4 by 2015. Adopting routine vitamin K by injection would help India reduce its high U5MR and in China further reduce its neonatal mortality, yielding a global impact in the fight to reduce child mortality.

Conclusions

Vitamin K prophylaxis is a well-established, safe and cost effective intervention for the prevention of VKDB in newborns in developed countries, yet the incidence and implications of vitamin K deficiency in developing countries has received little attention. The examples of India and China indicate that although China has had greater success in reducing U5MR at a faster rate than India, the proportion of neonatal deaths to under-five deaths remains a challenge to the Chinese public health system. While no reliable data are publicly available, the issue of VKDB is finally receiving attention from the Chinese public health system as well as the Indian government.

Not only in emerging countries or low-income countries, VKDB and its prevention is still a significant concern in high-income countries. Lack of proper laboratory test facilities to diagnose VKDB in developing countries and the failure to diagnose neonatal deaths may distort statistics, as late VKDB is often sudden in onset and the infant may die before reaching a hospital. However, vitamin K by injection is a safe, inexpensive and effective intervention and should be given to all newborns as a high priority in the public health policy of governments and international donor organizations. Even in high-income countries, parental refusal of recommended vitamin K injections at birth is resulting in a return of this preventable condition with serious morbidity and fatal results. In some high-income countries, choice of oral vitamin K administration is also a factor in the return of VKBD. But especially for low and medium-income countries, mandatory vitamin K injection following birth would be an effective addition to recommended interventions for global initiatives and agencies to help reduce preventable neonatal mortality and morbidity.

Funding: None.
Ethical approval: Not required.
Competing interest: The authors declare that they have no conflict of interest.
Contributors: Rai RK, Luo J, and Tulchinsky TH provided intellectual input through different stages of preparation of this manuscript equally.

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Received January 27, 2015
Accepted after revision April 1, 2015