

Parents' refusal to vitamin-K supplementation among neonates and its association with vaccine refusal: A systematic review and meta-analysis

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Abstract

Objective: This systematic review and meta-analysis aims to estimate the prevalence of neonatal vitamin K prophylaxis refusal among parents and its possible association with subsequent vaccine hesitancy or refusal.

Method: The databases searched included PubMed, Cochrane Library, Embase via Ovid, CINAHL Plus and Medline via EBSCOhost, ProQuest and PsycINFO from inception to 31 August 2017. Keywords, such as "vitamin K", "refusal", "decline", "hesitancy", and "vaccination" were used to identify potential studies. Analysis of proportions was conducted, while odd ratios and relative risks were estimated using the random effect model.

Results: Of the 2216 studies identified, 8(0.36%) were subjected to qualitative analysis; 4(50%) retrospective cohort studies and 4(50%) cross-sectional studies. Overall, 6(75%) studies were of good quality, while 2(25%) were ranked as of fair quality. Of the 273,714 parents, 3,136(1.14%) refused to opt for the vitamin K prophylaxis. Meta-analysis concluded that refusal to vitamin K prophylaxis was significant among the included studies ($p < 0.184$).

Conclusion: The overall risk of refusal to essential vaccination among vitamin K prophylaxis refusal group was 6.45 times compared to the group that accepted vitamin K prophylaxis.

Keywords: Vaccine hesitancy, Vitamin K prophylaxis, Vaccine refusal, Newborn, Parents. (JPMA 72: 2251; 2022)

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Introduction

Vitamin K is a fat-soluble vitamin which is required for synthesis of blood clotting factor II (pro-thrombin), VII, IX and X in the liver.¹ At birth, the plasma concentration of these vitamin K-depending clotting factors are very low and therefore newborns are susceptible to bleeding. Despite the fact that plasma level of vitamin K gradually increases by six weeks of age, prophylactic vitamin K is encouraged among newborns to prevent related complication.¹

Prophylactic administration of Vitamin K to newborns is an effective public health intervention to prevent Vitamin K deficiency bleeding (VKDB). Vitamin K can be administered in newborns via intramuscular (IM) injection or oral route for the prevention of VKDB.² VKDB is also known as the haemorrhagic disease of the newborn (HDN), which is characterised as bleeding in newborns in the first few weeks of life. Depending on the age of onset, VKDB is further classified into early (first 24 hours of life), classical (days 1-7) and late (after first week to 6 months).³ Generally, the bleeding sites include gastrointestinal and nasal lining.¹

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The incidence of early and classic VKDB without receiving any prophylaxis is 0.25% to 1.7% whereas the incidence of late VKDB is 4.4 to 7.2 per 100,000 infants.⁴ Unfortunately, many parents still choose to reject administration of vitamin K prophylaxis despite the known consequences.⁵

Vaccine hesitancy is one of the global concerns for the increased occurrence of vaccine preventable diseases. Vaccine hesitancy is defined as "delay in acceptance or refusal of vaccines despite the availability of vaccine services".⁶ Due to certain public doubts and controversy towards vaccination, parents may start opting against having their children vaccinated.⁷ This could significantly increase the risk to the lives of unvaccinated children due to absence of innate immunity which might lead to high mortality.

There is an ongoing discussion about the parents who refuse neonatal vitamin K prophylaxis as they may extend their doubts to essential vaccination and may refuse the required immunisation schedule for their children. A study in New Zealand has shown that parents' refusal for IM injection or oral vitamin K in the neonatal phase were more likely to refuse childhood vaccination.⁸ Another study conducted in Alberta, Canada, reported a similar association between neonatal vitamin K prophylaxis refusal with subsequent vaccination refusal.⁹ Keeping in view the importance of the matter, the current systematic review was planned to explore the prevalence and potential impact of the parent's decision on neonatal prophylaxis

vitamin K refusal. Besides, the findings may be used as an indicator to predict subsequent vaccine uptake or vaccine refusal/ hesitancy.⁹

Materials and Methods

The systematic review was comprised search on all the relevant scientific databases from their inception until August 31, 2017. The databases searched included PubMed, Cochrane Library, Embase via Ovid, CINAHL Plus and Medline via EBSCOhost, ProQuest and PsycINFO. Search strings were created using Boolean OR and AND to combine relevant keywords, such as vitamin K, refusal, decline, hesitancy, and vaccination to identify potential studies. Medical subject headings MeSH terms were used, such as vaccination and immunisation. Truncation technique was used for parent*, and key words parents and parental were included.

The studies included were experimental or observational studies published in English language which assessed neonatal IM injection or oral dose vitamin K refusal among parents, and which reported refusal to vaccine among the parents refusing vitamin K injection or oral supplementation. Systematic reviews, narrative reviews, letters to the editor, case reports, case series and personal opinions were excluded.

For the purpose of the current review, 'declined vitamin K' meant the parents had either declined IM injection or oral dose of vitamin K, 'declined all' was defined as refusal or failure to vaccinate at the mentioned schedule, and 'declined partial' meant those who declined some but not all vaccinations. Both 'declined all' or 'declined partial' were counted as 'declined vaccination'. Between the two studies^{8,9} which assessed the prevalence of parents who declined neonatal vitamin K as well as vaccination, only one study⁹ specified the type of vaccines that the parents had declined. Since the other study did not specify which vaccine the parents had declined, therefore, it was decided that any vaccine that the parents had declined were taken into account.

The primary outcome was to determine the prevalence of parents rejecting neonatal vitamin K prophylaxis, while the secondary outcome was to determine the likelihood of refusal to subsequent vaccination if the parents had rejected vitamin K prophylaxis initially.

Data relevant to study characteristics and outcomes of interest were extracted from the full-text papers. Newcastle Ottawa Quality Assessment Scale was used for accessing the quality of studies.¹⁰ For cohort studies, Newcastle Ottawa Scale for Cohort Studies was used to assess quality, whereas the Newcastle Ottawa Scale for Cross-sectional

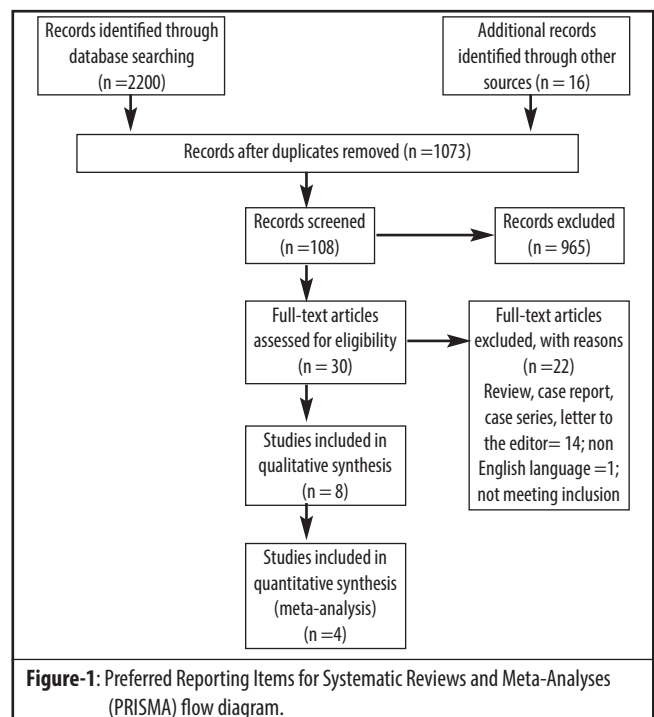
Studies was used to assess the quality of cross-sectional study. For each item, a score of 1 was awarded if the criterion was fulfilled. If the item was not applicable to the study, 'NA' [not applicable] was indicated and the item was awarded a score of 1. Overall score >7 graded a study in the category of 'good quality', 4-6 as 'fair quality' and <3 as 'poor quality'.

For missing/incomplete data regarding ethnicity and antenatal care, authors for studies^{8,11} were contacted, and they confirmed the incompleteness of data regarding ethnicity of parents. A study had already mentioned that there was missing data regarding primary attendant at birth.⁹

Data relevant to the outcomes of interest was used to perform meta-analysis. Analysis of proportions was conducted using STATA 14.2. Odds ratios (Ors) were estimated using the random effect model to estimate the overall effect at a confidence level of 95% to estimate the risk of vitamin K refusal among the parents from the included studies. Furthermore, relative risk (RR) was estimated to rule out the refusal to vitamin K prophylaxis as a potential factor leading to decline of essential vaccinations. In case heterogeneity was higher (>50%), subgroup analysis was performed to identify the causes of higher heterogeneity, Tau² was estimated to interpret statistical heterogeneity.

Results

Of the 2216 studies identified, 8(0.36%) were subjected to



qualitative analysis (Figure 1); 4(50%) retrospective cohort studies^{8,9,11,12} and 4(50%) cross-sectional studie.^{8,9,11,12} The highest number of studies found was on the ProQuest database 895(40.4%) (Table 1).

Most of the participants were Caucasian and some were Asian since all of the studies were conducted in western countries (Table 2). For the retrospective cohort studies, generally the participants' data was based on hospital record, birth centre and planned home birth.^{8,9,11,12} Furthermore, the most common birth mode were mainly

vaginal birth and others with assisted birth, such as caesarean section (CS).^{8,9,11,12} On the other hand, for the

Table-1: Databases searched and records found.

Databases	Number of Records
PubMed	394
Cochrane Library	11
Embase via Ovid	516
CINAHL Plus and Medline via EBSCO host	377
ProQuest	895
PsycINFO	23

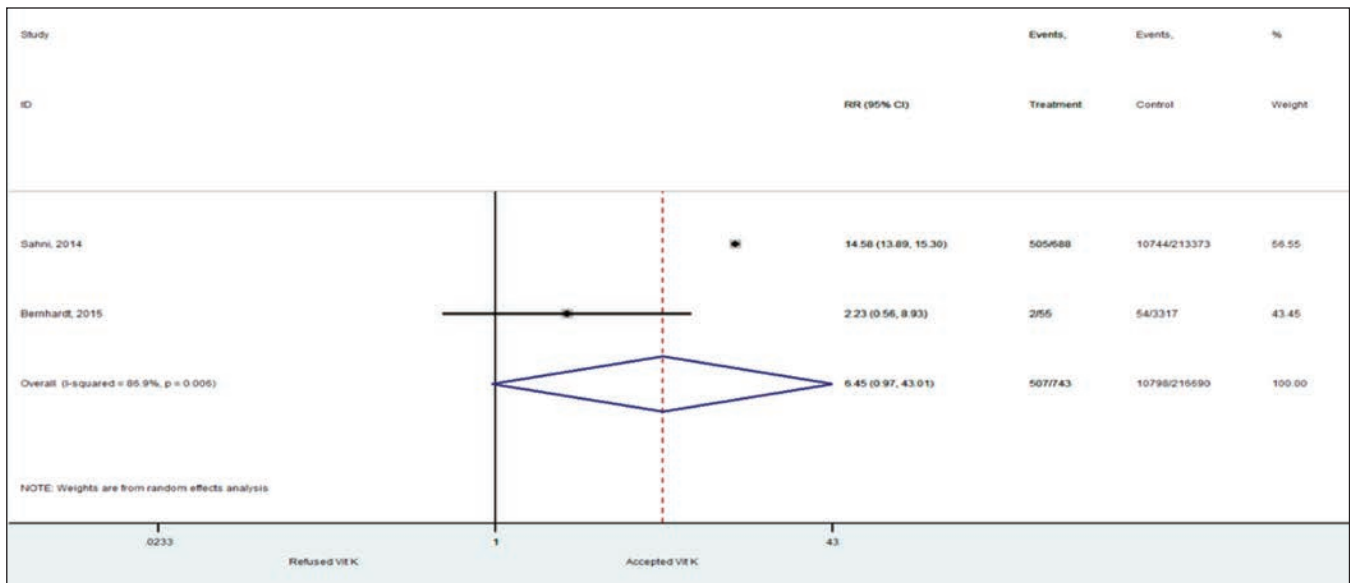


Figure-2: A Forest plot illustrating risk of vitamin K refusal and parents' decision for essential vaccination.

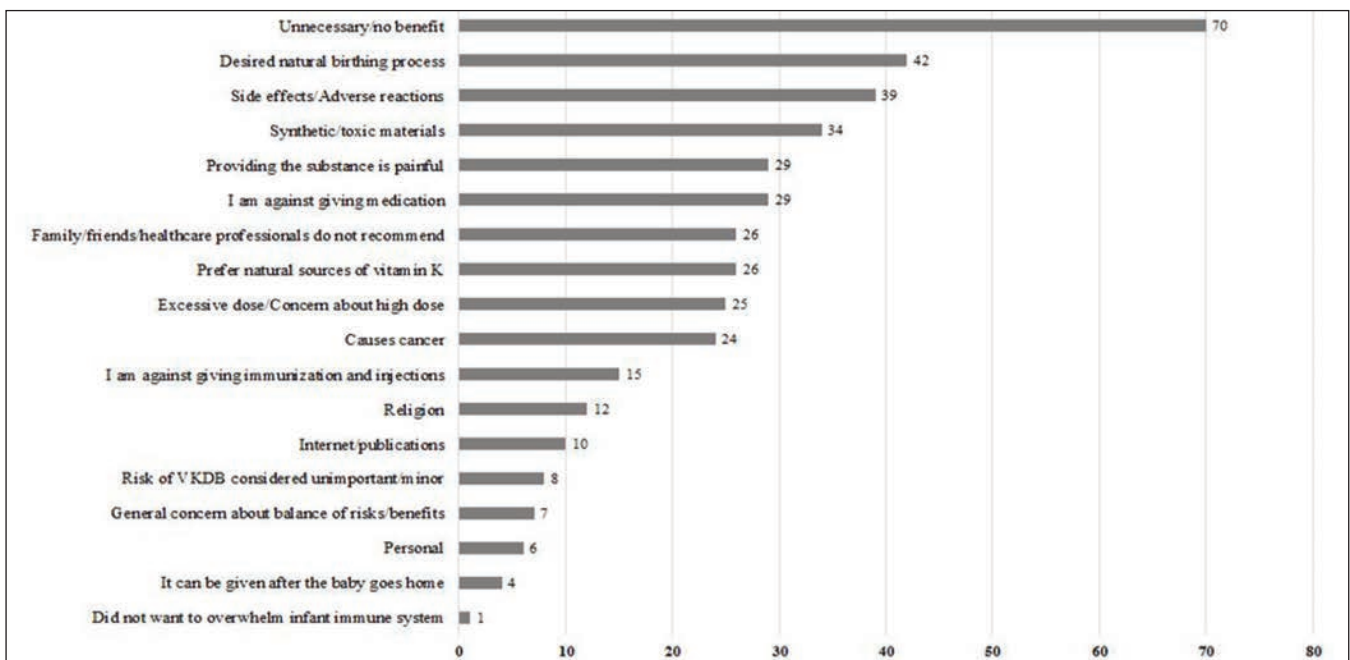


Figure-3: Common reasons for refusing vitamin K prophylaxis.

Table 2: Summary of the characteristics of the included studies.

First author, Year	Objective	Study design	Sample Size, n	Setting	Participants Ethnicity, n	Declined Vitamin K, n	Declined vaccination, n	Summary of findings	Quality score
Bernhardt, 2015 ⁸	Investigate parents who decline newborn vitamin K are also more likely to decline subsequent childhood immunisations.	Retrospective cohort	3575	New Zealand	NZ European: 2487 Other European: 282 NZ Maori: 207 Asian: 114 Pacific Islander: 93 Others: 382	74	14	Parents who declined newborn vitamin K are more likely to decline immunisation for their child with an increased risk ratio of 14.1.	7
Sahni, 2014 ³⁰	Characterize parents who are likely to decline newborn vitamin K and whose children are likely to be unimmunized.	Retrospective cohort	282378	Canada	Aboriginal: 20882 Non-Aboriginal: 261496	906	688	Vitamin K refusal was associated with a 14.6 higher relative risk of having no recommended childhood vaccines.	8
Burke, 2015 ¹¹	Describe rates of newborn vitamin K prophylaxis uptake according to method of administration (IM, oral, refused) and identify predictors for refusal of vitamin K prophylaxis.	Retrospective cohort	7009	New Zealand	European: 5320 Maori: 434 Pacific: 183 Asian/Indian: 304 MELAA: 73	119	NA	Refusal of vitamin K was associated with Asian ethnicity, vaginal delivery and gestational age, per additional week.	7
Khambalia, 2011 ¹²	Compare maternal and infant characteristics by mode of VK administration.	Retrospective cohort	281 678	Australia	Not Specified	3136	NA	IM injection was the most prevalent mode of administration. Compared to neonates receiving IM VK, those with oral or none were more likely to have vaginal births at birth centres or planned home births and were less likely to receive hepatitis B vaccination.	8
Eventov-Friedman, 2013 ¹³	Examine the knowledge, perceptions, cultural and religious barriers of expecting parents regarding vitamin K prophylaxis.	Cross-sectional	217	Israel	Not Specified	NA	NA	Two thirds had academic degrees, yet were ignorant regarding recommendation to provide vitamin K. Moreover, first-time parents had not yet decided to provide vitamin K after birth.	6
Hamrick, 2016 ²⁹	Examine factors influencing parents' decisions to refuse IM vitamin K prophylaxis.	Cross-sectional	54	United States	White: 42 Black: 6 Hispanic: 3 Other: 3	NA	NA	Parents who refused IM vitamin K often sought information especially the internet. 83% of parents reported awareness of risks associated with vitamin K refusal, however, only 11% decided to accept prophylaxis.	7

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Table 2: Continued from previous page.

First author, Year	Objective	Study design	Sample Size, n	Setting	Participants Ethnicity, n	Declined Vitamin K, n	Declined vaccination, n	Summary of findings	Quality score
Marcewicz, 2017 ³¹	Investigate vitamin K refusal among parents in 2013 at Nashville area hospitals and Tennessee birthing centers	Cross-sectional	207	United States	Not Specified	NA	NA	Vitamin K refusal was much higher at birthing centres. The most common responses for refusal were a belief that the injection was unnecessary and a desire for a natural birthing process.	7
Miller, 2016 ¹⁵	To explore the influencing factors and reasoning of parents who opt out of intramuscular vitamin K prophylaxis for their newborn.	Cross-sectional	15	New Zealand	NZ European: 8 Dutch: 1 Sinalese: 1 Russian: 1 English: 1 American: 1 Japanese: 1 Indian: 1	NA	NA	Parents opt out of intramuscular vitamin K due to parents' beliefs and values, concerns about their child's welfare and external influencing factors.	5

cross-sectional studies, the surveys were handed to parents or soon-to-become parents to explore their opinion towards vitamin K prophylaxis.^{5,13-15}

Overall, 6 (75%) studies were of good quality, while 2 (25%) were ranked as of fair quality. Regarding the sample size, the justified sample size was 5,000 for retrospective cohort study and 100 for cross-sectional study.

Based on the 4950 retrospective cohort studies, 4,235 newborns did not receive vitamin K prophylaxis due to parental refusal. Meta analysis showed that there were 273,714 parents, and 3136 (1.14%) of them refused to opt for vitamin K prophylaxis (Table 3).

Two (50%) of the studies^{8,9} reported that among the parents who rejected vitamin K at first, 702 children did not receive any vaccination or had partial vaccination. Both studies also revealed that parents who declined vitamin K injection were more likely to reject subsequent vaccination. Overall, the risk of not opting for essential vaccination for their children was observed to be 6.45 (95% confidence interval [CI]" 0.97-43.01) among the parents not refusing vitamin K prophylaxis ($p<0.006$). Refusal to essential vaccinations was noticed 2.23 times higher among the parents who accepted vitamin K one study and 14.57 times in the other study (Figure 2). Overall, the risk of refusing essential vaccination among parents refusing vitamin k prophylaxis was 6.45 times less than the parents accepting vitamin K prophylaxis (Figure 2).

Antenatal care by midwives contributed the most towards parental refusal; the incidence of rejection of vitamin K was most common in planned home birth and birth centres (Table 4). Generally, parents thought that the vitamin K prophylaxis for newborn had no benefit or unnecessary and preferred natural birthing process (Figure 3). There was only one study which determined the reasons for accepting vitamin K, and the most common reason was that the parents felt that the treatment was important to baby's health.¹³

Discussion

To the best of our knowledge, the current systematic review and meta-analysis is among the first to explore the association of unwillingness to neonatal vitamin K prophylaxis with subsequent vaccination refusal. Overall, meta-analysis showed that the chance of refusal to vitamin K supplementation was about 1% among the respondents of the selected studies. This number might look smaller because the total numbers of parents investigated in the included studies were 566,676. Conversely, among the parents who refused neonatal vitamin K prophylaxis, there were about 88% who actually declined to even the essential vaccinations. However, interpreting the association of vitamin K prophylaxis refusal to essential vaccination should consider the inconsistencies between the studies by.^{8,9} Both these studies are from different regions, and that have contributed to higher statistical heterogeneity ($p=0.006$). Moreover, difference in design, clinical setting and background of refusal to vaccination may have contributed to higher heterogeneity. However, it cannot be ignored that parents who refused vitamin K prophylaxis were very likely to reject subsequent

Table-3: Proportion of parents who declined vitamin K prophylaxis.

Analysis performed	Study	OR CI 95%	% weight	I ²	Tau ²	p-value
Overall analysis of four studies	Bernhardt, 2015 ⁸	0.021 [0.017 – 0.027]	24.75	99.8%	0.8119	<0.001
			25.15			
	Sahni, 2014 ³⁰	0.003 [0.003 – 0.003]	24.92			
	Burke, 2015 ¹¹		25.18			
	Khambalia, 2012 ¹²	0.017 [0.014 – 0.021]				
	Pooled odd ratio	0.012 [0.011 – 0.012]				
		0.011 [0.04 – 0.26]				
Subgroup analysis based on region/ country	Bernhardt, 2015 ⁸	0.021 [0.017 – 0.027]	24.75	43.2%	0.0088	0.184
			24.92			
	Burke, 2015 ¹¹	0.017 [0.014 – 0.021]	25.15			
	Pooled odd ratio	0.019 [0.015 – 0.023]	25.18			
<i>New Zealand</i>				99.9%	0.8987	<0.001
<i>Others (Canada/ Australia)</i>	Sahni, 2014 ³⁰					
	Khambalia, 2012 ¹²	0.003 [0.003 – 0.003]				
	Pooled odd ratio	0.012 [0.011 – 0.012]				
		0.011 [0.004 – 0.026]				

OR: Odds ratio, CI: Confidence interval.

1vaccinations. In this situation, even with the significant heterogeneity the current analysis highlighted the need to counter parental refusal to essential vaccinations.

The review discovered that parents who declined newborn vitamin K shared some noticeable characteristics, such as those who had received antenatal care from midwives. This could be possibly explained by a study which reported that 45% of the midwives were doubtful about newborn receiving vitamin K.¹⁶ Perhaps there is a need to explore the matter because midwives spend most time with parents as it could lead up to six weeks of postpartum care.⁸ Besides, the incidence of parents refusing neonatal vitamin K was most common at planned home birth and birth centres. This could be possible due to parents who desired a more natural birth experience.⁵ This is consistent with findings of¹⁴ to the effect that the choice of delivery sites may reflect parents' belief or attitude of healthcare providers and the way they counsel parents at these facilities.¹⁴

The review focussed on the association between newborn vitamin K refusal and subsequent vaccination, but put less emphasis on the route of administration of vitamin K. Nonetheless, there is an ongoing discussion regarding the route of administration of newborn vitamin K.¹⁷⁻¹⁹ IM injection and oral dose form have been claimed to be equally effective in preventing early VKDB, but IM injection is superior to oral preparation in the prevention of late VKDM.¹⁹ Therefore, the oral route of vitamin K may not be suitable in the prevention of late VKDB even in multi-dose regimens. Nevertheless, oral dose form of vitamin K is widely used in Europe.²⁰ In addition, the Canadian Paediatric Society has suggested providing oral dose of

vitamin K if the parents refused IM injection²¹ Perhaps all policy-makers should work together and come up with a standard guideline or practice for administrating vitamin K.

The current review noticed a few common reasons of rejecting neonatal vitamin K. However, multiple studies have proved no association between Vitamin K administration and childhood cancer.^{22,23} Parallel to Vitamin K, there are a few factors leading to vaccine refusal and the most common concern was fear of adverse side effects and vaccine safety.^{24,25} Generally, parents are

afraid of negative impact on child's immune system and serious side effects, such as autism. Other than that, parents are concerned about the presence of mercury 'thimerosal' in the vaccine.²⁴ The United States Food and Drug Administration (FDA) has clarified that all childhood vaccines formulation no longer contain thimerosal, with the exception of multi-dose influenza vaccine.²⁶ In fact, a meta-analysis has shown that thimerosal is not associated with the development of autism.²⁵

It is vital to provide education and training to healthcare providers, especially in communication skills in order to address parents' attitude towards vaccine hesitancy and specific serious adverse events following immunisation.⁸ Since the influence of healthcare providers on parents' decision-making regarding vaccination is substantial, it is important to address such a behaviour among healthcare providers as well. Other than healthcare professional students, providing education and knowledge about vaccination in younger individuals may also assist in shaping future vaccine beliefs and behaviours. The other strategy recommended to address vaccine hesitancy is social media approach.²⁷ The internet is the major source of information and communication tool in today's world.^{5,13} Therefore, the content of social media needs to be better monitored by the relevant authority.

Since there is a strong association between declining newborn vitamin K and subsequent vaccination, therefore, data from these developed countries on neonatal vitamin K refusal could be used as a useful indicator to predict subsequent vaccination refusal and this will assist the developing countries in improving their vaccination rates. Although there is only a small percentage of parents

Table 4: Characteristics of parents who rejected neonatal vitamin K prophylaxis.

First author, Year	Ethnicity, n (%)		Antenatal Care, n (%)			Birth location, n (%)			
	Physician	Midwife	Others	Hospital	Birth Centre	Planned birth	home	Others	
Bernhardt, 2015 ⁸	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	
Sahni, 2014 ³⁰	n=542 of whom 0.2% rejected vitK prophylaxis	318 of whom 6.77 rejected vitK prophylaxis	n=44 of whom 1.42% rejected vitK prophylaxis	648 of whom 0.2% rejected vitK prophylaxis	24 of whom 10.7% rejected vitK prophylaxis	216 of whom 14.5% rejected vitK prophylaxis	18 of whom 2.9% rejected vitK prophylaxis		
Burke, 2015 ¹¹	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	
Khambalia, 2012 ¹²	General practitioner: 245 (1%) Hospital based medical: 511 (1.2%) Private obstetrician: 398 (0.5%)	n=1455, of whom 1.9% rejected vitK prophylaxis	n=527 of whom 1.3% rejected vitK prophylaxis	n=2315 of whom 0.9% rejected vitK prophylaxis	n=357, of whom 4.4% rejected vitK prophylaxis	n=329, of whom 67.1% rejected vitK prophylaxis	n=135, of whom 2.8% rejected vitK prophylaxis		

declining newborn vitamin K, it is an excellent opportunity to identify this particular group of parents who are more likely to decline vaccination, and to provide them with proper education and counselling regarding vaccination [8,9]. Clinicians should use evidence-based and rational argument while approaching the parents.^{19,28} The current systematic review has its limitations, like language restriction as it included papers that were only in the English language. Besides, some of the studies had significantly larger sample size than the other, and this may affect the accuracy of overall conclusions.

Conclusion

Refusal to essential vaccination was 6.45 times higher among the parents who accepted vitamin K prophylaxis. It is challenging to ensure that all parents agree to have their newborns vaccinated with vitamin K prophylaxis and other vaccinations, but healthcare providers should try their best to be attentive towards parents' concerns and should educate them accordingly. On the other hand, parents should be aware of the appropriateness and reliability of information, especially from the internet sources.

Limitations: We have extracted all relevant scientific databases till 2018. We recently carried out a search query in PUBMED with the key words 'vitamin K' AND 'HESITANCY'. As we applied a filter of 2018 to 2022, only one qualitative study in this duration and no study was found relevant to our study design.

(<https://pubmed.ncbi.nlm.nih.gov/?term=%28Vitamin+K%29+AND+%28Hesitancy%29&filter=y&ears=2018-2022&timeline=expanded>)

Therefore, the current evidence produced in this systematic review and meta-analysis is sufficient to address the research question and objective set at the time of conception of the idea.

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Disclaimer: The text is based on an academic thesis submitted to the Monash University, Malaysia campus, for which it was submitted to Turnitin scan and Online Repository as a part of practice.

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