ORIGINAL PAPER

Nagoya J. Med. Sci. **80**. 11–20, 2018
doi:10.18999/nagjms.80.1.11

Estimated costs for treatment and prophylaxis of newborn vitamin K deficiency bleeding in Tashkent, Uzbekistan

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ABSTRACT

Vitamin K deficiency bleeding (VKDB) is a preventable cause of infant mortality and long-term morbidity through the world. This study aimed to demonstrate the costs of VKDB treatment estimated from the hospital records in Tashkent, Uzbekistan, as well as the prophylaxis costs for mass vitamin K medication. Subjects were 50 patients with no operation and 50 patients who had received a brain operation, consecutively enrolled from 180 cases diagnosed at Republican Research Center of Emergency Medicine in 2014. In that year, an additional 22 VKDB patients were found in Tashkent; the incidence of VKDB was 478/100,000 among 42,225 newborns. The prophylaxis costs for all newborns in Tashkent were estimated under a plausible condition. The average age at admission was 43.2 days among 100 patients (67 boys and 33 girls) with birth weight from 2,600 g to 3,800 g (3,105 g on average). The great majority of patients (92.0%) were breastfed; 89.5% in boys and 97.0% in girls. Average treatment cost per VKDB patient was 365 USD for the operated and 285 USD for the non-operated. Total expenses of the 202 patients were estimated to be 64,603 USD. A single prophylaxis was estimated to cost 1.24 USD, totaling 52,359 USD for the prophylaxis of 42,225 newborns. Since the reduction of VKDB incidence through prophylaxis is considered to be higher than 78.5% (52,359/64,603), provision of prophylaxis services would reduce the total costs of VKDB treatment in Uzbekistan, where prophylaxis is not provided.

Keywords: vitamin K deficiency, intracranial bleeding, prophylaxis, mortality, morbidity

INTRODUCTION

Vitamin K deficiency bleeding (VKDB) is a preventable cause of infant mortality and long-term morbidity.[1)] Vitamin K (VK) is a fat soluble vitamin stored in human fat tissue and the liver. There are two types of VK in nature. VK_1 is found in some plants, while VK_2 is normally produced by the human gut bacteria *Escherichia Coli*, except in newborn babies, as their digestive tract is sterile at birth. VK_3 is a synthetic type which has been used since the 1940s.[2)] VK has a role in blood clot or coagulation, as well as bone metabolism; thus its deficiency causes

Received: May 9, 2017; accepted: September 4, 2017
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VKDB, a very serious complication.

VKDB, also referred to as a hemorrhagic disease of the newborn, is a global problem. Bleeding disorders were first observed by Townsend, who reported 50 bleeding cases in newborns in 1894.[3] To prevent VKDB, the American Academy of Pediatrics recommended in 1961 that prophylaxis is necessary for all newborns.[2] Since 1982, use of routine oral VK prophylaxis has been increasing in the United Kingdom.[3] In Japan, VKDB has been decreasing since 1984 due to nationwide routine prophylaxis with VK.[4]

The main risk factors of VKDB have already been discovered; anticonvulsant and anticoagulant drugs taken by mothers, and malabsorption syndromes in babies, such as diarrhea, cystic fibrosis and liver diseases. Other reported risk factors are gender, birth order, birth weight, and breastfeeding.[2] One study in Taiwan reported 32 patients with VKDB, among whom the most common age at diagnosis was 10 to 40 days, the sex ratio of boys to girls was 2 to 1, 84% of babies were breastfed, and all patients had some degree of intracranial hemorrhage, with the mortality rate of 9.4%. All survivors except one suffered neurologic disabilities such as microcephaly, epilepsy, cerebral palsy, severe psychomotor retardation.[5] Another study in Turkey in 2013 reported similar results.[6]

Nationwide studies from developed countries in 1997 showed a median incidence of 7.1 per 100,000 (range 4.8 to 25) for late VKDB.[2] This rate decreased to 1.1 per 100,000 newborns in Netherlands after routine VK prophylaxis in 1992–94.[7] In Southeast Asian countries such as Thailand, Malaysia, Vietnam, and China, the incidence was 11 to 116 per 100,000 newborns in 1984–99.[8-10] A survey in New Zealand, which has prophylaxis service, showed that the incidence was 1 per 100,000 during 1998–2008, while the risk when there is no prophylaxis was estimated to be 66 times higher.[11] In Uzbekistan, nationwide data were not available at the time of this writing.

Although the problem of VKDB is still a subject of disputes and uncertainty,[12] parenteral VK prophylaxis is believed to be a useful public health measure. A study demonstrated that the benefits definitely outweighed the side-effects and costs.[13] Studies conducted in Germany and New Zealand showed that prophylaxis was cost-effective: the costs of preventing one case of VKDB were much lower than the expenses of treating a VKDB patient and taking care of a lifelong handicapped survivor.[2]

With the strong emphasis on prevention of diseases, the Millennium Development Goals (MDG) developed by Uzbekistan in 2006 also put forward several public health aims to achieve better health conditions for the Uzbek population. The criteria for selecting priorities indicated that the emphasis should be on health problems with the greatest morbidity, disability and premature death, as well as on the risk factors amendable through public health activities. As declared in MDG 4, actions should be taken to decrease the mortality rate of newborns by preventing common fatal diseases among infants.[14] In recent years, Uzbekistan, like many other countries mentioned above, is facing a growing problem of infant mortality and disability caused by VKDB. The number of cases of VKDB has been growing rapidly. In 2012, the Pediatric Intensive Care Department of Republican Research Center of Emergency Medicine (RRCEM) reported 50 cases of VKDB with intracranial bleeding, which tripled to 151 in 2014. As a result, costs of treating the affected patients and caring for the disabled survivors have been skyrocketing year by year. Without routine prophylaxis, the cost is likely to grow even more, costing huge amounts of money for the healthcare budget, which is financed by the central government. This study aimed to illustrate the costs of treatment of VKDB patients and prophylaxis in Tashkent Uzbekistan, based on hospital records and vital statistics on birth.

MATERIALS AND METHODS

Subjects

In 2014, 202 VKDB newborns were found in Tashkent among 42,225 live births; 180 at RRCEM, 13 at Children Hospital No.1 (CH1), and 9 at Mother and Child Hospital (MCH). Among these 202 patients, 151 patients had intracranial hemorrhage and another 51 patients had bleeding in different sites (post injection, intestine and nose). Among them 88 patients (43.6%) were operated on, 103 patients (51.0%) were treated without operation, and 11 patients (5.4%) died in hospital. For the purpose of easier cost calculation, 50 patients with operation and 50 patients without operation out of 180 patients admitted in 2014 were consecutively selected at RRCEM. All 100 patients had brain hematoma and considerable degree of bleeding in the brain. One non-operated patient out of the 100 patients died soon after arriving at hospital. Five possible risk factors were collected: sex, age at admission, weight at birth, birth order, and milk feeding (breast-fed, bottle-fed, or mixed).

The ethical approval was obtained from the Department of Protecting Motherhood and Childhood, the Ministry of Health of Uzbekistan. Since this study was based on the anonymized records, consent was not obtained from the patient's parents.

Cost estimation

Based on medical reports, patients' expenses for tests (laboratory and imaging), medications, operations, and anesthesia were calculated from the first day in hospital until discharge. Medical service expenses documented on patient medical reports were calculated based on the prices fixed by the RRCEM in 2014. Using the state budget, the RRCEM provided these medical services free of charge to patients. In order to calculate test expenses, at first all the information on diagnostic tests from the patient records of RRCEM were collected, including general blood analysis, coagulogram, biochemical analysis, urine analysis, feces analysis, X-ray, ultrasound diagnosis, and computer tomography. Secondly, the average number of times checked per patient was calculated and then multiplied by the cost of one time analysis. Then, the information of treatment was collected from medical charts. In RRCEM, the treatments were fully standardized.

The VK prophylaxis was assumed to be an intramuscular VK injection within 6 hours after birth; 0.5 mg for babies with birth weight 1,500 g or less and 1.0 mg for babies with birth weight more than 1,500 g. The cost of prophylaxis for one newborn was estimated as follows. VK was 2,000 SOM (0.75 USD), and syringe and needle was 400 SOM (0.15 USD). The prices were fixed by the pharmaceutical committee in 2014. In 2014, a full-time nurse earned 345,600 SOM per month. Usually, one nurse works 8 hours per day, 24 days per month (6 days per week), totally 192 working hours per month. The amount of monthly salary was divided by 192 working hours and resulted in 1,800 SOM per hour, 900 SOM (0.34 USD) for half an hour. In total, the prophylaxis cost was set to be 3,300 SOM (1.24 USD). The total cost for the prophylaxis was obtained by the cost for one newborn multiplied with the number of babies in 2014.

Statistical analysis

Mean, standard deviation, minimum, and maximum were calculated for continuous variables. For the percentages, 95% confidence interval (CI) was calculated based on a binomial distribution. A Manna-Whitney test were used to analyze differences in age, weight, birth order and feeding type between male and female patients. Statistical Package for Social Sciences (SPSS) version 22.0 was used for these analysis.

RESULTS

This study identified 202 VKDB patients among 42,225 alive births in 2014 at the three hospitals. The incidence rate was 478 per 100,000 live births (95% CI, 415 to 548 per 100,000). Table 1 shows the characteristics of 100 selected patients at RRCEM. There were more boys (67.0%) with VKDB than girls (33.0%), with a ratio of 2 to 1. The majority of newborns'

Table 1 Characteristics of patients with vitamin K deficiency bleeding at Republican Research Center of Emergency Medicine in Tashkent, Uzbekistan, 2014

	Male	Female	Total	P value[a]
	N (%)	*N* (%)	*N* (%)	
Total	67 (100)	33 (100)	100 (100)	
Age at admission (days)				
<30	18 (26.8)	9 (27.3)	27 (27.0)	0.134
31–60	44 (65.7)	21 (63.6)	65 (65.0)	
61–90	4 (6.0)	3 (9.1)	7 (7.0)	
91–120	1 (1.0)	0 (0.0)	1 (1.0)	
Weight (g) at birth				
2,500–3,000	15 (22.4)	9 (27.2)	24 (24.0)	0.644
3,000–3,500	49 (73.1)	19 (57.6)	68 (68.0)	
>3,500	3 (4.5)	5 (15.2)	8 (8.0)	
Birth order				
1st	42 (62.7)	26 (78.8)	68 (68.0)	0.107
2nd	19 (28.3)	5 (15.1)	24 (24.0)	
3rd	5 (7.5)	2 (6.1)	7 (7.0)	
4th	1 (1.5)	0 (0.0)	1 (1.0)	
Milk feeding				
Breast-fed	60 (89.5)	32 (97.0)	92 (92.0)	0.200
Bottle-fed	2 (3.0)	0 (0.0)	2 (2.0)	
Mix	5 (7.5)	1 (3.0)	6 (6.0)	

[a]Mann Whitney-U test for age, weight and birth order, and χ^2 test for milk feeding.

age (days) when hospitalized at onset was between 30–61 days (65.0%). Newborns with birth weight 3,000–3,500 g were 68.0%. Among the subjects, 68.0% of newborns were the first-born children, 24.0% were the second-born, 7.0% of babies were the third-born, and one baby was the fourth-born. The largest number of infants (92.0%) were breast-fed, only 2 babies were bottle-fed, and remaining 6 newborns was mixed (breast-fed and bottle-fed).

As shown in Table 2, mean age at admission was 43.2 days, minimum age was 20 days, and maximum age was 120 days. Mean weight at birth was 3,105 g, minimum weight 2,600 g,

Table 2 Average, standard deviation (SD), minimum (Min), and maximum (Max) of age, weight and bed days according to treatment mode

	Operated (N = 50)				Non-operated (N = 50)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Age (days)	41.8	12.8	20	70	44.7	18.5	20	120
Weight (g)	3,096	220.1	2,600	3,550	3,113	266.5	2,650	3,800
Bed days	25.2	15.8	7	107	19.5	16.7	1	97

Table 3 Average and standard deviation (SD) of test and treatment cost (SOM) per one operated vitamin K deficiency bleeding patient in 2014, Tashkent, Uzbekistan

Test	Times checked		Cost of one time analysis	Average cost for one patient
	Mean	SD		
General blood analysis	9.2	2.6	9,057	83,868
Coagulogram	4.3	1.7	45,647	193,543
Biochemical analysis	2.8	2.2	65,315	180,269
Urine analysis	2.7	1.9	6,610	17,186
Feces analysis	2.4	1.5	7,431	18,429
X-ray	1.3	0.6	17,398	16,006
Ultrasound diagnosis	1.5	0.6	19,916	27,484
Computer tomography	2.4	1.2	72,710	174,504
Total				711,290
Treatment	**Average quantity of medicine**		**Cost of one unit**	**Average cost for one patient**
	Mean	SD		
Antibiotics (Ceftriakson)	22.5	12.5	1,415/1flk	31,894
Vikasol	4.6	0.5	502/1tab	2,329
Benzonal	25.2	15.8	90/1tab	2,272
Fresh freezing Plasma	1.3	0.5	45,405/150ml	60,843
Packed red blood cells	1.0	0.0	22,900/100ml	22,900
Solution (NaCl 0.9% + KCl 4% + $MgSO_4$ 25%)	20.2	10.9	2,801	56,364
Catheter F3	1.0	0.0	28,499	28,499
Operative expenses	1.0	0.0	30,000	30,000
Anesthesiological expenses	1.0	0.0	25,000	25,000
Total				260,101

[a]Average bed days of operated patients with VKDB were 25.2 days

[b]1 USD = 2,663 SOM

maximum weight 3,800 g, and standard deviation 243 g. The patients needed to stay in hospital for 22.3 days on average (25.2 days for operated and 19.5 days for non-operated patients). The longest stay was 107 days, while the shortest was 1 day for the case wherein death occurred due to severe bleeding and serious complications shortly after admission.

Table 3 shows the average expenditure for tests and treatment per one operated VKDB patient. The tests, such as all blood tests, brain scan, ultrasound diagnosis, X-ray, urinary test, etc., per one operated patient constituted on average 711,290 SOM (267 USD). Expenses of treatment including medicine and operation per one operated patient cost 260,101 SOM (98 USD) on average.

Table 4 illustrates the average tests and treatment expenses per one non-operated patient with VKDB. The diagnostics such as all blood tests, brain scan, ultrasound diagnosis, x-ray, urinary test, etc., per one non-operated patient cost 613,589 SOM (230 USD) on average. Expenses treatment per one non-operated patient cost 145,676 SOM (55 USD) on average.

Fig. 1 demonstrates the individual costs of tests and treatments for the operated and non-operated within the admission period. The minimum cost was 237,440 SOM (89.16 USD) for the patient who died soon after the admission, while maximum was 2,026,210 SOM for the patient admitted for 107 days. Table 5 demonstrates the estimated costs for treatment of VKDB in 2014 and expected costs for prophylaxis for all newborn with VK in the same year. The

Table 4 Average and standard deviation (SD) of test and treatment cost (SOM) per non-operated vitamin K deficiency bleeding patient in 2014, Tashkent, Uzbekistan

Type of test	Times checked		Cost of one time analysis	Average cost for one patient
	Mean	SD		
General blood analysis	7.3	3.2	9,057	66,116
Coagulogram	3.5	1.6	45,647	159,765
Biochemical analysis	2.7	1.9	65,315	173,738
Urine analysis	2.4	1.5	6,610	14,278
Feces analysis	2.0	1.2	7,431	14,416
X-ray	1.4	1.1	17,398	20,182
Ultrasound diagnosis	1.3	0.6	19,916	25,492
Computer tomography	1.9	1.1	72,710	139,603
Total				613,589
Treatment	**Average quantity of medicine**		**Cost of one unit**	**Average cost for one patient**
	Mean	SD		
Antibiotics (Ceftriakson)	17.1	14.5	1,415/flk	24,281
Vikasol	4.0	0.8	502/tab	2,018
Benzonal	17.4	11.8	90/tab	1,571
Fresh freezing Plasma	1.1	0.3	45,405/150 ml	52,670
Packed red blood cells	1.0	0.0	22,900/100 ml	22,900
Solution (NaCl 0.9% + KCl 4% + $MgSO_4$ 25%)	14.7	10.2	2,801	41,399
Intravenous cannulas	1.0	0.0	837	837
Total				145,676

[a]Average bed days of non-operated patients with VKDB were 19.5 days

[b]1 USD = 2,663 SOM

average expenses per one operated VKDB patient from the first day in hospital until discharge were 971,371 SOM (365 USD), and those per one non-operated VKDB patient were 759,266 SOM (285 USD). Total expenses were estimated to be 85,480,648 SOM (32,099 USD) for 88

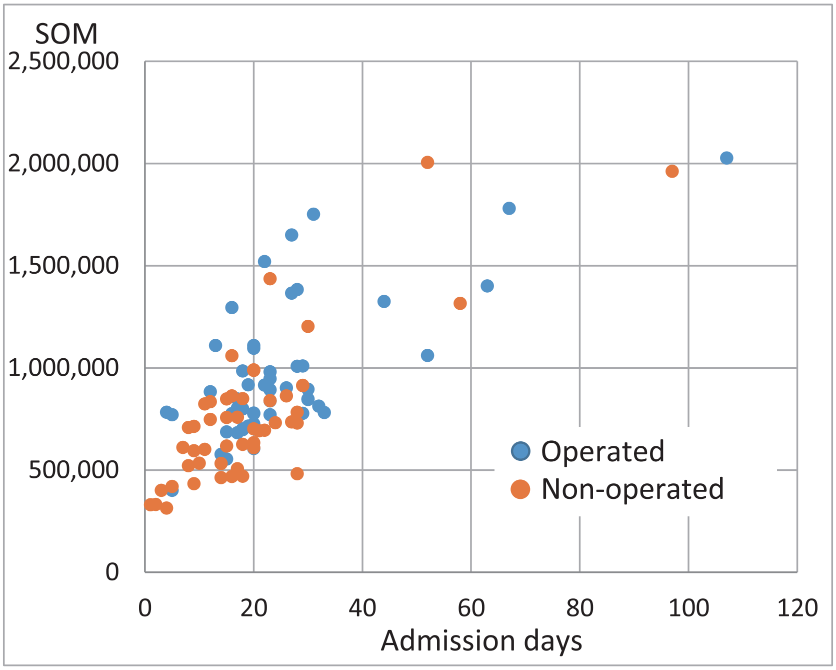

Fig. 1 Individual costs of tests and treatments for the operated and non-operated with the admission period

Table 5 Estimated costs for treatments of vitamin K deficiency bleeding (VKDB) in 2014 and expected costs for prophylaxis for all newborns with vitamin K in Tashkent, Uzbekistan

	Treatment for 202 patients[a]			Prophylaxis for 42,225 babies[b]
	Operated (N = 88)	Non-operated (N = 114)	Operated & Non-operated (N = 202)	
In SOM				
1 patient	971,371	759,266		3,300[c]
All patients	85,480,648	86,556,340	172,036,988	139,342,500
In USD[d]				
1 patient	365	285		1.24
All patients	32,099	32,503	64,603	52,325

[a]All reported patients in Tashkent city, 2014 (three pediatric hospitals)
[b]Born in Tashkent city, 2014 from Republican Government Statistical Centre
[c]Fixed costs for vitamin K, syringe, needle, and nurses service by State Pharmaceutical Committee in 2014
[d]1 USD = 2,663 SOM

operated patients and 86,556,340 SOM (32,503 USD) for 114 non-operated patients. In total, the costs was 172,036,340 SOM (64,603 USD) for the tests and treatment of the 202 patients. The expenses for single prophylaxis including VK, syringe, needle and nurse's service were calculated to be 3,300 SOM (1.24 USD), as described in MATERIALS AND METHODS. The costs for the prophylaxis would be 139,342,500 SOM (52,325 USD) for 42,225 babies in Tashkent.

DISCUSSION

The VK administration to newborns is routinely conducted in many countries. In the United States, Canada, and Australia, the recommended administration is 0.5 mg to 1.0 mg of VK with intramuscular injection, while three times of oral administration is recommended in the guideline of Japan Pediatric Society (http://www.jpeds.or.jp/uploads/files/saisin_110131.pdf). In Uzbekistan, the corresponding recommendation was in preparation at the time of this writing.

Generally, VKDBs are divided into 3 groups; early VKDB (from birth to 24 hours), classic type (from 1 day to 7 days), and late VKDB (more than one week). Late type VKDB can be observed in infants from 8 days to 6 months, with the most common age being from 21 to 60 days.[15] Early VKDB is frequently associated with anticoagulant or anticonvulsant medicines used by mothers during pregnancy, while classical and late VKDB are attributed to the absence of VK prophylaxis.[16] The great majority of babies in this study were at the common age of late VKDB, suggesting that all the patients in this study had late VKDB. In late VKDB, one of the main risk factors is breastfeeding in addition to the absence of VK prophylaxis.[1,6,15,16] In this study, the average age of VKDB patients at admission was 43.3 days.

The vast majority of previous studies illustrated that this disease occurs more in boys than girls.[5,7] The present study showed a 2-to-1 boy-girl ratio, which was a similar ratio to that in the other studies on VK deficiency. Although there was no control group in this study for the estimation of the risk, most of the babies were the first children in their families. Previous studies in Thailand and Japan reported a similar finding.[17,18] The average birth weight was normal (3,105 g) among the subjects. As late VKDB occurs after 20 days, presumably, birth weight may not be an influencing factor.

The estimated treatment expenses for all 202 patients were about 172 million SOM (64,600 USD), while the prophylaxis cost for all newborns in Tashkent was estimated to be about 139 million SOM (52,000 USD). The total cost of prophylaxis was 81.0% of the cost for diagnosis and treatment of VKDB. Previous research reported that the effectiveness of VK prophylaxis was 97% with intramuscular injection (IM) and 80% with oral VK prophylaxis.[19] In this study, 95% confidence interval of the VKDB incidence was 415–548 per 100,000. If prophylaxis with 97% effectiveness were introduced in Tashkent city, the incidence could be reduced to 12–16 per 100,000 live births, i.e., 5 to 7 out of 42,225 newborns. For the 6 newborns with VKDB, only 5,110,010 SOM (1,919 USD) would be needed. Adding the amount to the costs of prophylaxis, the total expenditure would be 144,452,510 SOM (54,244 USD); the benefit would be about 28 million SOM (10,000 USD), in addition to saved lives and prevented disabilities. These figures were estimated only for the capital, Tashkent city. There are 12 regions and an autonomic republic in Uzbekistan. Based on these calculations, we might be able to economize a huge amount of the healthcare budget if prophylaxis were carried out in the whole country.

As demonstrated in this study, breastfeeding is very common in Uzbekistan. Breastfeeding is an integral part of culture, and Uzbek women tend to use bottle feed only in exceptional conditions, such as health problems of the mother or baby. According to a study in Uzbekistan, 2001, 90% mothers breastfed their children.[20] This high percentage of breastfeeding may explain the high incidence rate of VKDB in Uzbekistan (478/100,000 in Tashkent). Under these conditions, VK prophylaxis appears to be urgently necessary in Uzbekistan.

This was the first study to document the costs of treatment and prophylaxis of VKDB, as well as the estimated costs of prophylaxis against VKDB in Uzbekistan. The figures of expenses used for calculations were those standardized by the government. However, there were several limitations. First, the costs of treatment were not calculated for all 202 VKDB patients in 2014. However, the costs per one case might not differ largely from the estimates based on all 202 cases, because the 100 patients were selected consecutively among the operated patients and non-operated patients. Secondly, the nurses' salaries were added to calculate the cost of VK prophylaxis, while those of doctors and nurses salaries were not included for the treatment costs. It would not be feasible to calculate the salaries of the medical staff for VKDB, which should be added to the treatment costs. Thirdly, the patients were not followed to evaluate longer term costs due to disabilities, which should be accounted for the costs of no prophylaxis. This study demonstrated that the costs of prophylaxis were less expensive than treatment costs even in terms of short-term costs. Fourthly, 51 patients with non-cranial bleeding were not included in the 100 subjects for cost calculation. The costs for treatment of non-cranial bleeding might be cheaper because of shorter bed days and no surgical treatment including multiple pre- and post-operation tests, medications/anesthesia and longer-term rehabilitation. Since non-cranial bleeding patients were classified into non-operated patients, the estimated total costs for 202 patients could slightly be overestimated. Lastly, this study did not take account of the refusal rate of the prophylaxis treatment. The reported rate was 0.39% in Canada, 2012.[21,22] The rate in Uzbekistan would be negligible if the prophylaxis service were covered by government in a mandatory manner.

As stated above, medical services are provided at public hospitals by the government of Uzbekistan, where almost all hospitals are public. The prices used in the calculation of medical service expenses are fixed by the government's healthcare budget. Since the routine prophylaxis of VKDB for newborns would also be provided by the government, less expensive services with an effect to reduce the disease burden should be selected. The prophylaxis would save many of children from death and long-term neurological disabilities caused by the complications of VKDB. Introducing routine prophylaxis of VKDB is strongly recommended in Uzbekistan.

ACKNOWLEDGEMENTS

We would like to thank Dr. S. Ismoilov, Director of Protecting Motherhood and Childhood Department, Ministry of Health in Uzbekistan for his recommendation and ethical approval letters. We are also thankful to Dr. A. Hadjibaev, Director of Republican Research Center of Emergency Medicine for his support.

COMPETING INTEREST

The authors declare that they have no competing interests.

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