Original Research Article

A Retrospective Study on Clinical Features and Aetiology of Early Neonatal Jaundice in Term Babies at Ratchaburi Hospital, Thailand

ABSTRACT

Background: Neonatal jaundice is a common condition that sometimes leads to devastating neurological consequence such as kernicterus. This study was aimed to find out the clinical features and etiology of neonatal jaundice in term newborn admitted to Ratchaburi Hospital.
Aim: This study was aimed to recognize clinical features and to know etiology of term neonatal jaundice.
Study design: Hospital-based retrospective study
Methodology: The study was conducted by reviewing 117 medical records of neonatal jaundice who were admitted at Ratchaburi Regional Hospital, Bangkok, Thailand from 1st October 2007 to 30th September 2008. Both the patient's and their mother's profiles, etiology and clinical features of jaundice were extracted.
Results: The results showed that female babies were more likely to develop jaundice. The most common etiology was inconclusive jaundice (64.9%) followed by ABO incompatibility (17.9%) and breastfeeding jaundice (10.2%)., Other less common causes were G6PD deficiency, minor blood group incompatibility and cephalhematoma. The onset of neonatal jaundice usually occurred on the 2nd to the 4th day of life and almost all newborns responded well to phototherapy. Most of the interventions were started on the 2nd day of life and exchange transfusion was needed in four cases.
CONCLUSION: **FROM OUR STUDY, THE MOST COMMON ETIOLOGY OF JAUNDICE WAS INCONCLUSIVE JAUNDICE WHICH IS FOLLOWED BY ABO INCOMPATIBILITY BUT NON-IMMUNE HEMOLYSIS AND POLYCYTHEMIA WERE NOT ENCOUNTERED. THERE WAS SIGNIFICANT DIFFERENCE OF HAEMATOCRIT, NRC AND RETICULOCYTES BETWEEN HAEMOLYTIC AND NON-HAEMOLYTIC GROUPS. DETAILED APPROACH TO HISTORY TAKING AND PHYSICAL EXAMINATION, EARLY INVESTIGATIONS OF JAUNDICE AND SEPTIC WORK UP ARE RECOMMENDED IN ELICITING VARIOUS ETIOLOGIES AND PREVENTING COMPLICATIONS.**

Keywords: Neonatal jaundice, etiology, clinical feature, retrospective

1. INTRODUCTION

The most common cause of readmission to hospital in healthy term infants is neonatal jaundice [1]. Paediatricians were aggressive in treating jaundice though several factors have changed the management of jaundice [2, 3]. Effective approach and evaluations for management are crucial in preventing bilirubin-induced encephalopathy and long term neurodevelopment outcomes [4]. The possible factors exaggerating physiological jaundice are shown in table 1 [5].

Table 1: Possible factors exaggerating physiological jaundice

Factor	Clinical correlate
1. Bilirubin load to liver	• Infants with polycythemia • Infants of a diabetic mother • Collection of extravasated blood like cephalhematoma and intraventricular haemorrhage • Delayed cord clamping
2. Defective uptake from liver	• Decreased Y protein due to caloric deprivation
3. Defective bilirubin conjugation	• Due to decreased UDPG activity as seen in hypothyroidism and inhibitors in breast milk
4. Deceased hepatic excretion	• Congenital infections
5. Inadequate hepatic perfusion	• Hypoxia • Congenital heart diseases
6. Increased enterohepatic circulation	• Unfed babies • Delayed passage of meconium

Studies in the 1980s and 1990s suggested that kernicterus from jaundice was rare and that too many infants were being treated unnecessarily [6, 7]
Early detection, effective intervention and new approaches to prevention have also been stimulated as hyperbilirubinaemia is potentially damaging to developing brain [8]. Previous studies have indicated a relationship between neonatal hyperbilirubinemia and diverse factors including racial region, male gender, epidural anaesthesia, and instrumental delivery [9].

Risk factors for significant neonatal hyperbilirubinemia are:

1. Jaundice visible on the first day of life
2. A sibling of jaundice or anaemia
3. Unrecognized haemolysis (ABO, Rh and another blood incompatibility)
4. Non optimal feeding (Formula or breastfeeding)
5. Deficiency of glucose 6 phosphate dehydrogenase
6. Infection, Infant of diabetic mother and immaturity
7. Cephalhematoma or bruise, Central haematocrit >65% (polycythemia)
8. East Asian, Mediterranean, Native American heritage [10].

Pathological Jaundice fulfils any of the following criteria:

1. Clinical jaundice appearing in the first 24 hours.
2. Increase on the level of total bilirubin by more than 0.5 mg/dL/hr or 5mg/dL/24 hr.
3. Total serum bilirubin > 12 mg/dL in term infants and total serum bilirubin level 10- 14 mg/dL in preterm infants (Almeida, 2004).
4. Direct reacting bilirubin > 2.0 mg/dL [11].

The primary concern with respect to exaggerated hyperbilirubinemia is the potential for neurotoxic effects, but general cellular injury also occurs [12]. Bilirubin can interfere with neuroexcitatory signals, impair nerve conduction (particularly auditory nerve) inhibit exchange and water transport in renal cells. Infections, acidosis, hypoxia, sepsis, prematurity and hyperosmolarity can increase blood-brain barrier susceptiblity to the entry of bilirubin [13].

Risk factors of severe hyperbilirubinemia: [14]

Major Risk Factors:

1. Pre-discharge micro bilirubin level in the high-risk zone
2. Jaundice observed in 1st 24 hour
3. Blood group incompatibility with a positive direct antiglobulin test, another known haemolytic disease
4. The previous sibling received phototherapy
5. Cephalhematoma or significant bruising
6. Exclusive breastfeeding if nursing is not going well (poor lactation).
7. East Asian Race

Minor Risk Factors:

1. Pre-discharge micro bilirubinemia level in the high intermediate risk zone
2. Jaundice observed before discharge
3. Previous sibling with jaundice
4. Macrosomic infant of a diabetic mother
5. Male Gender

Factors associated with decreased risk of neonatal jaundice

1. Microbilirubin level in the low-risk zone
2. Exclusive bottle feeding with adequate lactation
3. Black race
4. Discharge from the hospital after 72 hour

Although hazardous hyperbilirubinemia (≥ 30mg/dL) is uncommon, timely recognition, comprehensive work up and appropriate management play pivotal roles in the prevention of chronic, bilirubin-induced neurotoxicity [15]. This study aimed to document the clinical profiles and aetiology of early neonatal jaundice.

2. MATERIAL AND METHODS

This study was a hospital-based retrospective study of 117 medical records, conducted at Ratchaburi regional hospital, Bangkok, Thailand from November 2008 to March 2009. The clinical features of early neonatal jaundiced for newborns younger than 7 days and whose gestational age ranges from 37 to 42 weeks were explored and the onset of jaundice within 7 days requiring intervention for jaundice was studied. The sample size was calculated using the formula for single population proportion with the margin of error 10%, the assumption of 95% confidence level [20] and prevalence of 60% of known etiology of neonatal jaundice in all pathological jaundice in Ratchaburi Regional Hospital. The minimum sample size required was 92. The exclusion criteria included preterm, low birth weights, major congenital anomalies and congenital infections, systemic infections before the onset of jaundice, serious illness such as sepsis, meconium aspiration syndrome, and severe birth asphyxia. Required data from the selected records were collected and transferred into case record forms that were constructed based upon the variables from Ratchaburi Regional Hospital and study objectives. The data obtained were analysed using SPSS version 11.5. The research was funded by the Faculty of Tropical Medicine, Mahidol University, Thailand in collaboration with SEAMEO TROPMED, Thailand.

3. RESULTS

Figure 1 shows that inconclusive jaundice (jaundice of unknown cause) was the most common in this study (n=76, 64.9%), which was followed by ABO incompatibility (17.9%). Other diagnoses were breastfeeding jaundice (10.2%), G6PD deficiency (4.2%) and minor blood group incompatibility (1.7%). There was one case of cephalhaematoma and there were no cases of non-immune haemolysis and polycythemia in this study.

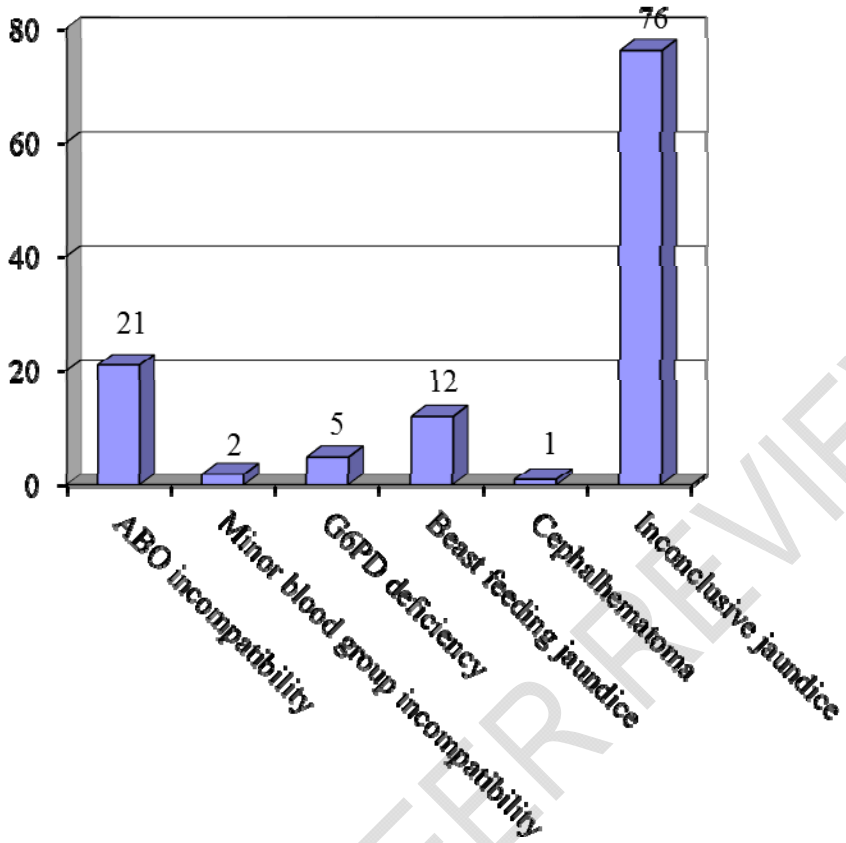

Figure 1: Etiologies of Jaundice

Table 2: Characteristic maternal profile according to the etiology of jaundice

Maternal profile	No.	Blood group incompatibility		G6PD def. (n=5)	Breastfeeding (n=12)	Cephal-hematoma (n=1)	Inconclusive (n=76)
		ABO (n=21)	Minor (n=2)				
Maternal age (n=113)							
15-20 years	26	5	0	0	1	0	20
21-35 years	76	15	2	5	7	1	47
36-45 years	11	1	0	0	4	0	6
Maternal complication (n=116)							
CPD	18	5	0	1	1	0	11
Hypertension	2	0	0	0	0	0	2
Diabetic	1	0	0	0	1	0	0
Hypertension and diabetic	1	0	0	0	0	0	1
No complication	94	16	2	3	10	1	62
Oxytocin using (n=115)							
Yes	3	0	0	0	0	0	3
No	112	21	2	5	11	1	72
Any medication during pregnancy (n=115)							

Yes	2	0	0	0	1	0	1
No	113	21	2	4	11	1	74
Previous neonatal jaundice history (n=67)							
Yes	5	0	0	0	1	0	4
No	62	13	0	4	5	1	39

Table 2 shows that 47/76 cases (62%) born to mothers aged between 21 to 35 years were diagnosed as inconclusive jaundice. In this study, oxytocin was used in 3 mothers and diagnoses of their infants were inconclusive jaundice. Among 5 cases that had the previous history of neonatal jaundice, 1 case was breastfeeding jaundice and other 4 cases were inconclusive jaundice. Other findings such as bruise/petechiae, hepatosplenomegaly were not observed in this study.

Table 3: Maximum bilirubin level according to the etiology of jaundice

Maximum bilirubin level	No.	Blood group incompatibility		G6PD def. (n=5)	Breastfeeding (n=12)	Cephal-hematoma (n=1)	Inconclusive (n=76)
		ABO (n=21)	Minor (n=2)				
Maximum micro bilirubin level (mg/dL)							
<12	5	0	0	0	1	0	4
12-25	106	21	2	5	11	1	66
>25	6	0	0	0	0	0	6
Maximum unconjugated bilirubin level (mg/dL)							
<12	10	1	0	0	1	0	8
12-25	103	20	2	5	11	1	64
>25	4	0	0	0	0	0	4

Most of the cases had the maximum micro bilirubin level in range 12-25 mg/dL. Similarly, the majority of the cases had a maximum unconjugated bilirubin level of 12-25 mg/dL. All cases that had bilirubin level above 25 were in inconclusive etiology group. (Table 3)

Table 4 shows the mean values of CBC profile and bilirubin levels according to etiology of hyperbilirubineemia. Maximum mean hematocrit (58.3%) was seen in babies with breastfeeding jaundice. In all diagnoses, the mean value of WBC and platelet count were within normal limit. NRC was found in only ABO incompatibility and inconclusive jaundice with a higher mean of NRC in ABO incompatibility (131.5%). Mean of reticulocyte count percentage was 13.6 in minor blood group incompatibility which was the highest in all etiologies. Mean value of conjugated bilirubin was highest (0.7 mg/dL) in ABO incompatibility while unconjugated bilirubin level was highest in minor blood group incompatibility (17.6 mg/dL). G6PD deficiency had the highest maximum value of micro bilirubin (20.5 mg/dL) among other causes of neonatal jaundice. Only one blood film had a hypochromic picture and this was in the inconclusive diagnosis group. Almost all patients had a normal size of red blood cells. Anisocytosis accounted for 11.9% and microcytes were 3.4%. On the other hand, only 11% of newborns had a normal shape of red blood cells. The rest 89% of them had an abnormal shape such as poikilocytosis, burr cells, target cells, spherocyte, ovalocyte, schistocyte and polychromasia.

As shown in Table 5, the onset of jaundice was most commonly on the 2nd day after delivery (n=49; 41.9%). It was followed by the 3rd day after birth (n=35; 29.9%) and the 4th day (n=12; 10.3%). Early onset jaundice (within 24 hours after birth) was seen in 10 cases (8.5%) and most of them (70%) were inconclusive jaundice. One case of breastfeeding jaundice and 5

cases of inconclusive jaundice presented with late onset of jaundice on the 6th and 7th day of birth. Late-onset neonatal hyperbilirubinemia was defined as significant hyperbilirubinaemia occurring between 5-7 days of life. According to the onset of jaundice, treatment was started mostly on the 2nd day after birth. Duration of phototherapy ranged from 1 to 4 days. There were four cases that needed exchange transfusion therapy for rescue. One case was ABO incompatibility with the onset of jaundice on the second day of life, micro bilirubin level was 16.4 mg/dL and reticulocyte count was 14.9%. Three cases were inconclusive jaundice with the onset of jaundice on the 2nd, the 4th and the 5th day and the micro bilirubin levels were 38.5, 32.9 and 31.1 mg/dL respectively, without evidence of haemolysis. For ABO incompatibility (n=21), all had blood group O mothers and blood group A and group B in newborn were 10 (47.6%) and 11 (52.4%) respectively.

Table 6 shows that the mean value of the maximum and minimum haematocrit was significantly lower in the haemolysis group than in a non-haemolysis group (P= 0.013 and P<0.001). Nucleated red cells (NRC) count and percent of reticulocyte counts were higher in haemolysis group than in a non-haemolysis group and the difference was statistically significant. Three cases were inconclusive jaundice with the onset of jaundice on the 2nd, the 4th and the 5th day and the micro bilirubin level were 38.5, 32.9 and 31.1 mg/dL respectively, without evidence of haemolysis.

Table 4: Laboratory profile according to the etiology of jaundice

Laboratory profile (Mean; Range; SD)	Blood group incompatibility		G6PD def. (n=5)	Breastfeeding (n=12)	Inconclusive (n=76)
	ABO (n=21)	Minor (n=2)			
CBC profile					
Maximum of Hct (%)	53.1	54.5	58.2	58.3	56.4
	38-68	48-61	52-70	50-66	32-70
	(7.3)	(9.2)	(7.2)	(5.9)	(6.7)
Minimum of Hct (%)	43.9	47.5	51.6	51.1	49.9
	31-57	38-57	47-63	38-60	30-62
	(7.4)	(13.4)	(6.5)	(6.6)	(7.1)
WBC count ($X10^3/mm^3$)	14.4	14.8	11.6	13.3	15.9
	6.9-24.5	13.9-15.7	7.8-20.5	9.1-20.5	6.0-17.3
	(4.7)	(1.3)	(5.1)	(3.6)	(23.3)
Platelet count ($X10^3/mm^3$)	291.0	345.5	234.8	236.3	275.8
	145-494	314-377	165-357	66-398	89-599
	(93.6)	(44.5)	(89.9)	(98.7)	(84.2)
NRC ($/mm^3$)	131.5	0	0	0	9.9
	0-1470				0-232
	(321.4)				(40.5)
% Reticulocyte count	8.6	13.6	4.6	7.1	6.0
	3-14.9	3.5-23.6	2.8-8.0	0.7-13.4	0-15.1
	(3.8)	(14.2)	(2.4)	(4.1)	(3.4)
Bilirubin					
Conjugated (mg/dL)	0.7	0.3	0.4	0.4	0.5
	0.2-6.0	0.3-0.4	0.2-0.4	0.2-0.7	0.0-10.6
	(1.2)	(0.0)	(0.1)	(0.2)	(1.2)
Unconjugated (mg/dL)	16.0	17.6	16.6	15.6	16.8
	11.9-21.4	16.4-18.8	12.4-21.1	9.4-19.1	7.3-37.8
	(2.6)	(1.7)	(3.7)	(2.8)	(4.9)

Maximum of MB	17.4 12.4-24.1 (2.8)	18.1 17.5-18.7 (0.8)	20.5 17.7-22.2 (1.9)	17.1 10.3-21.5 (3.0)	18.3 8.9-38.5 (4.9)

Table 5: Onset and treatment of neonatal jaundice

Characteristic of jaundice	No.	Blood group incompatibility		G6PD def. (n=5)	Breastfeeding (n=12)	Cephal-hematoma (n=1)	Inconclusive (n=76)
		ABO (n=21)	Minor (n=2)				
ONSET OF JAUNDICE							
1st day of birth	10	2	0	0	1	0	7
2nd day of birth	49	14	1	4	6	0	24
3rd day of birth	35	5	0	0	3	1	26
4th day of birth	12	0	1	1	1	0	9
5th day of birth	5	0	0	0	0	0	5
6th day of birth	1	0	0	0	0	0	1
7th day of birth	5	0	0	0	1	0	4
TREATMENT							
Day of start therapy							
1st day of birth	10	2	0	0	1	0	7
2nd day of birth	51	15	2	4	6	0	24
3rd day of birth	32	3	0	0	3	0	26
4th day of birth	11	0	0	1	1	0	9
5th day of birth	4	0	0	0	0	0	4
6th day of birth	3	1	0	0	0	0	2
7th day of birth	4	0	0	0	1	0	3
8th day of birth	2	0	0	0	0	1	1
Phototherapy duration (Days) (Mean; Range; SD)							
Single phototherapy		1.4 0-2 (0.6)	1	1.2 1-2 (0.4)	1.3 0-3 (0.9)	1	1.1 0-4 (0.7)
Double phototherapy		0.5 0-2 (0.7)	1 0-2 (1.4)	0.8 0-1 (0.4)	0.3 0-1 (0.5)	0	0.5 0-2 (0.7)
All type		1.9 1-4 (0.7)	2.0 1-3 (1.4)	2.0 1-3 (0.7)	1.7 1-4 (1.0)	1	1.6 1-6 (0.9)
Exchange transfusion	4	1	0	0	0	0	3

Table 6: Laboratory profile according to etiology of jaundice

Laboratory	Haemolysis (n=24)	Non-haemolysis	P value

CBC profile			
Maximum of Hct (%)	53.0 38-68 (7.2)	56.8 32-70 (6.5)	0.013
Minimum of Hct (%)	44.2 31-57 (7.7)	50.1 30-63 (6.9)	<0.001
WBC count (X10^3/mm^3)	14.5 6.9-24.5 (4.4)	15.3 6.0-17.3 (21.2)	>0.05
Platelet count (X10^3/mm^3)	304.1 145-497 (98.1)	265.4 66-599 (83.4)	>0.05
NRC count (/mm^3)	115.0 0-1470 (303.0)	8.1 0-232 (36.8)	0.001
% Reticulocyte count	8.7 3.0-23-6 (4.9)	6.0 0-15.1 (3.5)	0.003
Bilirubin			
Conjugated (m/dL)	0.7 0.16-6.0 (1.2)	0.5 0-10.6 (1.1)	>0.05
Unconjugated (m/dL)	16.4 11.9-21.4 (2.7)	16.6 7.3-37.8 (4.6)	>0.05
Maximum of MB	17.6 12.4-24.1 (2.7)	18.2 8.9-38.5 (4.6)	>0.05

4. DISCUSSION

This study was conducted to describe the various clinical profiles of early neonatal jaundice. According to the exclusion criteria of the current study, preterm babies with neonatal jaundice were not studied.

It is crucial to assess characteristic maternal and neonatal profile during the hospital stay and on discharge for risk of neonatal jaundice [16].

Previous research showed inconclusive jaundice was the most common aetiology as demonstrated in our study. Among various etiologies of neonatal jaundice in term babies, the most common etiology was inconclusive jaundice. This was probably because data was obtained retrospectively from medical records. Further septic work up and investigations are required to identify the accurate diagnoses in some of these cases. For instance high WBC count in inconclusive jaundice supports the possibility of neonatal sepsis and infections that are also the main concern for neonatal jaundice.

In our study, there was no difference between haemolysis and non-haemolysis group according to spontaneous delivery which was similar to a previous study finding [17]. Increased frequency of jaundice is obviously associated with maternal usage of epidural

anaesthesia. We did not encounter this in our study. We found that the minimum haematocrit was significantly lower and reticulocyte count was significantly higher in the haemolytic group compared to the non-haemolytic group which were compatible with the pathogenesis of hyperbilirubinemia. [18].

According to etiologies and maternal profile, nearly 50% of ABO incompatibility is primigravida in this study which is similar to the previous study establishing that approximately 50% of the ABO haemolytic jaundice cases occur in first-born infants and there is no predictable pattern of recurrence in subsequent infants [19]. Rh haemolytic disease and sepsis are associated with increased risk of bilirubin encephalopathy compared to ABO incompatibility [20].

Theoretically, G6PD deficiency usually occurs in males although heterozygous females may manifest the mild features of disease [21]. In our study, newborns diagnosed as G6PD deficiency were all males (4.2%).

Infection is one of the risk factors of hyperbilirubinemia [22]. Unexplained unconjugated hyperbilirubinemia may be the first sign of neonatal sepsis as bacterial sepsis can contribute to neonatal jaundice [23]. Our study did not demonstrate a higher WBC count in the non-haemolytic group compared to the haemolytic group. One of the possible explanations was that unidentified non-infectious etiologies may also play a significant role in the aetiology of non-haemolytic jaundice.

Measuring serum bilirubin concentrations exactly 24hours after delivery or at a later time just before discharge may improve the sensitivity of this predictor for hyperbilirubinemia [24]. Predictive bilirubin nomogram is an effective predictor for significant hyperbilirubinemia according to their risks; high, intermediate and low [25].

Among four cases for whom exchange transfusion was done, one case was ABO incompatibility and the rest three cases were inconclusive jaundice. Three cases of inconclusive jaundice had no evidence of haemolysis and onset of jaundice were on 2nd, 4th and 5th day while the micro bilirubin levels were 38.5, 32.9 and 31.1 mg/dL respectively. All neonatal jaundice with high bilirubin levels would require aggressive treatment (such as exchange transfusion and double phototherapy) to prevent complications of hyperbilirubinemia [26]. In a newborn with bilirubin level above 20 mg/dL, there is a noticeable association with kernicterus which has 70% risk of long term consequences [27].

One of our study limitations is that only term neonates were considered. As prematurity is one of the main causes of neonatal jaundice, further research with different inclusion criteria is suggested. As the study was the hospital-based retrospective record review, important data such as progression of jaundice and other clinical findings were not obtained. For a more comprehensive data, a prospective study is suggested.

5. CONCLUSION

From our study, the most common etiology was inconclusive jaundice which is followed by ABO incompatibility but non-immune hemolysis and polycythemia were not encountered. There was significant difference of haematocrit, NRC and reticulocytes between haemolytic and non-haemolytic groups. Detailed approach to history taking and physical examination as well as early investigations of jaundice including septic work up are recommended in eliciting various etiologies and preventing complications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

CONSENT

NA

ETHICAL APPROVAL

This research was approved and funded by the Faculty of Tropical Medicine, Mahidol University, Thailand.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

Here is the Definitions section. This is an optional section.

Term: Definition for the term