

NEONATAL DENGUE INFECTION: REPORT OF THREE CASES

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INTRODUCTION

Dengue infection has become a major public health problem in tropical regions. Dengue virus (DENV) is spread by mosquitos, causing variable manifestations, ranging from asymptomatic infection to flulike illness in dengue fever and sometimes severe hemorrhage or plasma leakage resulting in shock and death in dengue hemorrhagic fever (DHF).^{1,2}

The resurgence of dengue infection has been associated with an increasing incidence of dengue infection in adults with reports of dengue illness in pregnant women with transplacental transmission. Although a rare clinical occurrence, transplacental or vertical transmission of DENV may impose adverse effect on the fetus and give consequences to neonate, from asymptomatic to symptomatic clinical manifestation.^{2,3,4}

As Indonesia is an endemic area of dengue infection, there is a possibility that pregnant women may be infected with dengue virus. Incidence of dengue hemorrhagic fever in Indonesia at 2012 was 90.245 cases with 0.88% of mortality. Reported cases of dengue virus infection are rare in neonate and also not widely reported. No data about neonatal dengue infection has been reported in Indonesia. There were only 2 cases of neonatal dengue fever has been reported in RSUD dr. Soetomo.^{1,2,5}

Dengue in neonate can infect newborn due to vertical transmission or acquired through mosquito bites during neonatal period. Pregnant women and newborn's symptoms vary among the case reports published in the literature, however in general, the most common symptoms include fever and thrombocytopenia.^{4,6}

Infact of dengue may initially after the newborn presenting a clinical picture similar to neonatal sepsis and the period of time the disease takes to develop in newborn is usually between 5 until 13 days of life, that is after hospital discharge. Thus leading the case not being diagnosed as dengue and be managed as neonatal sepsis. More over cases of neonatal dengue infection might not be registered or diagnosed.^{1,6}

We report three cases of dengue virus infection in neonates on diagnosis and management along with a brief review.

CASE 1

Baby 1, a 3 day-old newborn baby girl, came with complaint of sudden and persisted fever for 2 days. The fever was approximately 38.7°C. She was exclusively breastfed but suck poorly. There was no complaint of dyspnea, cough, diarrhea, and seizure. She was born at term by spontaneous delivery with birth weight of 2,700g and length of 50 cm and an Apgar Score of 8 at 1st minute and 9 at 5th minutes post delivery. Routine intramuscular dose of vitamin K was administered.

On physical examination during admission, she was alert, fussy, and look icteric. She was 2,400g, with 158 beat per minute of pulse, 40 times per minute of respiration rate, 39°C of body temperature. Head examination showed jaundice was Kramer I-II, no anemia, cyanosis, nor dyspnea. Both of ears were normal. The neck was normal. The thorax examination also within normal limit which no retraction. The abdomen was flat, the bowel sound and movement was normal without palpable liver and spleen. The motoric strength and physiological reflexes were normal. The extremities were warm with capillary refill times less than 2 seconds. Physical examination revealed good circulatory perfusion and there was no associated rash or bleeding tendency.

Baby 1 was assessed as suspicious of neonatal sepsis with neonatorum jaundice. She was transferred to nursery ward for close monitoring of her illness. The first complete blood count (CBC) showed hemoglobin was 19.4g/dL, hematocrit was 52%, white blood cell count was 10,200/mm³ with 42% polymorphonuclear cells, 46% atypical lymphocytes, and platelet count was 75,000/mm³. Direct bilirubin was 0.6 mL/dL (0.1-0.5mL/dL) with total bilirubin was 5.5 mg/dL (0.5-1.0mg/dL). C-reactive protein was normal and blood also taken for blood culture.

She was treated initially with intravenous ampicillin sulbactam 100mg/kg of body weight/day divided into 2 doses, infusion of dextrose 10% 0.18 normal saline for fluid maintenance, oral feeding with breastmilk, and thermoregulation.

On the following day (3rd day of illness), fever persisted ranging from 37.8°C to 38.2°C. Further information revealed that her mother had complaint of mild arthralgia along with myalgia, and headache become severe after parturition. Mother's history of illness was taken.

A 24 year old mother, with the history of delivery at 38/39 week gestation, G1P0000, previously well and with an uneventful antenatal history without complaint of fever. She was subsequently admitted to the antenatal ward of for abdominal pain and vaginal discharge.

She was in well condition and no complaint of fever. The only complaint was mild arthralgia along with myalgia, and headache. Her blood pressure, body temperature, and heart rate were normal. Abdominal examination showed her uterine size corresponded to term pregnancy, the baby was in good condition. Other systemic examinations were essentially normal. An antenatal ultrasound was done which did not reveal any abnormality.

She was in active labour. Complete blood count at admission showed hemoglobin was 12.3 g/dL, hematocrit was 36%, white blood cell count was 9,200/mm³ with 27% of atypical lymphocytes, and platelet count was 307,000/mm³. Baby was born by spontaneous vaginal delivery with good Apgar Score. The amniotic fluid was clear. After delivery, she was discharge with good condition.

On 3rd day of baby's illness, mother's vital sign and physical examination were normal. Complete blood count showed hemoglobin was 12.4 g/dL, hematocrit was 37%, white blood cell count was 13,400/mm³ with 29% of atypical lymphocytes, and platelet count was 349,000/mm³. She stayed in an area which is known to have high transmission of dengue virus, whereas there was some people in her residential area have been diagnosed got dengue virus infection. Though, no other family members came down with similar illness.

According to this evidence, the serology tests of anti dengue immunoglobulin G (IgG) and immunoglobulin M (IgM) were examined. The result was positive of anti dengue IgG higher than IgM, indicating secondary dengue infection. The polymerase chain reaction (PCR) result was positive for dengue type 3 (DEN-3). Mother was diagnosed as having dengue virus infection. Mother did not have any complaint and was in good condition.

Based on her mother's history of illness baby 1 was evaluated for the possibility of virus infection, and accordingly a serial blood count was performed. The result of complete blood count showed hemoglobin was 18.1g/dL, hematocrit was 50%, white

blood cell count was 8,800/mm³ with 63% polymorphonuclear cells, 36% atypical lymphocytes, and platelet count was 92,000/mm³. The non structural 1 (NS1) antigen was done and the result was negative. Enzyme-linked immunoassay (EIA) revealed an increase in both anti dengue immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, whereas IgM increased higher than IgG, indicating primary infection. The polymerase chain reaction (PCR) result was positive for dengue type 3. Baby 1 was diagnosed with dengue fever.



On 4th day of illness, the fever was improved but there were some periods of fever increased. She was in stable condition without manifestation of bleeding. But the icteric still persisted, with the result of direct bilirubin was 0.7mg/dL and total bilirubin was 12mg/dL. Laboratory examination for TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes) infection by serology test of immunoglobulin M and G revealed positive result for IgG of rubella and IgG of CMV with high avidity. Laboratory examinations of HbsAg (hepatitis B surface antigen), anti HAV (hepatitis A virus), and anti HCV (hepatitis c virus) were negative.

On the following day, she could suck properly, so the intravenous fluid was stopped. The blood culture results were negative for bacterial growth. The antibiotic were discontinued after 5 days of treatment.

On 6th day of illness, the icteric was also improved. The result of complete blood count showed hemoglobin was 19.3g/dL, hematocrit was 53%, white blood cell count was 9,200/mm³ with 51% polymorphonuclear cells, 41% atypical lymphocytes, and platelet count was 200,600/mm³. Her serial complete blood examination and laboratory tests for dengue diagnostics were shown in Table 1. She discharged on good condition at 6th day of illness.

In case 1 there was evidence of dengue virus infection in both baby and mother, reflecting a vertical transmission of dengue virus from mother to baby summarized. Baby's and mother's vital sign and complete blood count were in Table 1.

Table 1. Temperature and serial complete blood counts of Case 1

	Before delivery	Born day	3 rd day fever [†]	4 th day fever [†]	5 th day fever [†]	6 th day fever [†]	7 th day fever ^{††}
Mother							
37.2 °C							
37 °C							
36.5 °C							
36 °C							
White blood cell(mm ⁻³)	9,200	-	13,200	-	-	-	-
Neutrophils (%)	68	-	64	-	-	-	-
Lymphocytes (%)	27	-	29	-	-	-	-
Platelets (10 ³ /mm ³)	307	-	349	-	-	-	-
Haemoglobin (g/dL)	12.3	-	12.4	-	-	-	-
Haematocrit (%)	36	-	37	-	-	-	-
IgM/IgG dengue			pos/pos				
NS-1			neg				
PCR-DEN 3							
Baby							
39°C							
38 °C							
37 °C							
36.5 °C							
36 °C							
White blood cell(mm ⁻³)		17,200	10,200	8,800	10,300	8,900	9,200
Neutrophils (%)		66	42	63	51	41	51
Lymphocytes (%)		18	46	36	34	40	41
Platelets (10 ³ /mm ³)		293	75	92	227	213	200
Haemoglobin (g/dL)		20.1	19.4	18.1	22.9	21	19.3
Haematocrit (%)		53	52	50	62	57	53
IgM/IgG dengue				pos/pos			
NS-1				neg			
PCR-DEN 3							

†day fever of baby

CASE 2

Baby 2, a 3 day-old new born baby boy, came with complaint of sudden fever for 1 day. The fever was approximately 39°C. There was no complaint of dyspnea, cough, diarrhea, and seizure. The mother had fever for 2 days before delivery. He was born at term by cesarean section with birth weight of 3,000g, length of 49 cm, and an Apgar Score of 7 at 1st minute and 9 at 5th minute post delivery. Routine intramuscular dose of vitamin K was administered.

On physical examination, he was alert, fussy, and responded well to oral feeding. He was 3,200 gram, with 150 beat per minutes of pulse, 46 times per minute of

respiration rate, 39°C of body temperature. Examination of head, thorax, abdomen, and extremities were within normal limit. The liver and spleen were not palpable. The motoric strength and the physiological reflexes were normal. The extremities were warm with capillary refill times less than 2 seconds. Skin perfusion was normal.

Baby 2 was assessed as suspicious of neonatal sepsis. He was transferred to nursery ward for close observation.

From laboratory examination revealed hemoglobin was 14.4 g/dl, hematocrit was 39.8%, white blood cell count was 8,000/mm³, and platelet count was 174,000/mm³. Blood culture was planned but unfortunately the parents refuse due to financial problem. He was treated with ampicillin sulbactam 100mg/kgbw/day divided into 2 doses was administered intravenously, also got oral feeding and thermoregulation.

On the following day (3rd day of illness), the average of body temperature reaching a peak of 38.5-39.1°C. Baby had stable vital sign and good oral feeding. On 4th day of illness, the temperature still persisted at 39.1°C.

On 5th day of illness, he couldn't feed well on his bottle and not doing well but he was alert and fussy. The temperature was 36.5-37°C, other vital sign within normal limit. Examination of head, thorax, abdomen, and extremity also normal. The extremities were warm, skin perfusion was normal. From laboratory examination revealed hemoglobin was 13.7g/dL, hematocrit was 39.4%, white blood cell count was 15,800/mm³, and the platelet count was 18,000/mm³. C-reactive protein was 14.8 mg/L (normal was < 6mg/L). There was no associated rash or bleeding tendency. For therapy we added intravenous fluid dextrose 10% 0.18 normal saline for fluid maintenance and other treatment was continued.

The history of previous illness from his mother during, and after delivery was taken. A 21 years old mother, G₁P₀₀₀₀, had experienced sudden febrile illness for 4 days before delivery. The pregnancy was at 39/40 weeks gestation. She complained of fever, headache, backache, myalgia, nausea, vomiting, and frequent uterine contractions. Her temperature was 39.8°C, pulse was 98 times per minute, respiration was 24 times per minute, and blood pressure was 90/60 mmHg. The fetal heart rate was 177 beat per minute. Her fetus was regularly monitored with serial sonography a non stress test on

the fetus showed a normal reactive response. The other systemic examinations were essentially normal.

Mother's complete blood count revealed hemoglobin was 10.9 g/dL, hematocrit was 32.4%, white blood cell count was 5,000/mm³, and platelet count was 131,000/mm³. Ampicillin was administered intravenously and also thermoregulation. Fever persisted without obvious clinical focus. On active labour, her temperature was 37.5°C. The white blood cell count was 8,000/mm³, platelet count was 198,000/mm³. Caesarean section was performed without any complication. There was no history of premature rupture of the membrane, amniotic fluid was clear. Two days after the operation, the mother's white blood cell count was 8,200/mm³ and platelet count was 126,000/mm³. The mother stayed in an area with high transmission of dengue virus and some people have been diagnosed with dengue infection. According to the evidence, physical examination, and laboratory result, mother was suspected of having a dengue fever. Serology tests of anti dengue IgM and IgG was positive, indicating secondary dengue infection. Her following clinical course was uneventful without sign of bleeding, plasma leakage, or hemodynamic instability. According to the history of illness the diagnosis of dengue fever can be established.


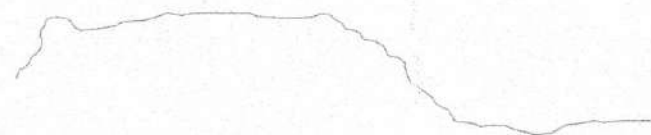
According to mother's history of illness baby 2 was suspected with dengue fever. His blood was taken for laboratory confirmation of dengue virus infection. Complete blood count revealed hemoglobin was 14.2 g/dL, hematocrit was 39.7 %, white blood cell count was 14,600/mm³, and platelet count was 54,000/mm³. Serology tests of anti dengue IgM was positive with negative result of anti dengue IgG indicating primary infection. The PCR was not performed. Baby 2 was diagnosed as having dengue fever.

On 7th day of baby's illness, the fever was improved also baby could feed properly. Mother was also getting better. There was no sign of plasma leakage or bleeding. Ampicillin sulbactam and intravenous fluid was stopped from his treatment because his clinical status was improved. The baby was in active and good condition. He made an uneventful recovery and was discharged on 9th day of illness.

In case 2 there was evidence that both baby and mother suffered from dengue virus infection. Vertical transmission of dengue virus from mother to baby was likely in

this case. Baby's and mother's vital sign and complete blood count are shown in Table 2.

Table 2. Temperature and serial complete blood counts of Case 2

	4days fever*	born day	1 st day fever†	2 nd day fever†	3 rd day fever†	5 th day fever†	6 th day fever†
Mother							
40 °C							
38 °C							
37.5 °C							
37 °C							
36.5 °C							
36 °C							
White blood cell(mm ⁻³)	5,000	8,000	13,200	8,200	-	-	-
Neutrophils (%)	-	-	64	-	-	-	-
Lymphocytes (%)	-	-	29	-	-	-	-
Platelets (10 ³ /mm ³)	131	198	349	126	-	-	-
Haemoglobin (g/dL)	10.9	-	12.4	-	-	-	-
Haematocrit (%)	32.4	-	37	-	-	-	-
IgM/IgG dengue							pos/pos
NS-1							
Baby							
39 °C							
38 °C							
37 °C							
36.5 °C							
36 °C							
White blood cell(mm ⁻³)			8,000			15,800	14,600
Neutrophils (%)			-			-	-
Lymphocytes (%)			-			-	-
Platelets (10 ³ /mm ³)			174			18	54
Haemoglobin (g/dL)			14.4			13.7	14.2
Haematocrit (%)			39.8			39.4	39.7
IgM/IgG dengue							pos/neg
NS-1							

*day fever of mother

†day fever of baby

CASE 3

Baby 3, a 14 day-old newborn baby girl, came with complaint of sudden fever for 2 days. The fever was approximately 39.5°C. She was exclusively breastfed but suck poorly and vomiting. She was well, active and tolerating breastfeeding till day 14 of life when she developed high grade fever. There was no complaint of dyspnea, cough, diarrhea, and seizure. She was normal term baby girl was born by spontaneous delivery with a birth weight of 2,700g and length of 50 cm and an Apgar score of 8 at 1st minute and 9 at 5th minutes post delivery. Routine intramuscular dose of vitamin K was administered.

On physical examination when admission, she was alert but fussy at examination. She was 2,600g, with 150 beat per minute of heart rate, 40 times per minute of respiratory rate, 40°C of body temperature. Head, thorax, abdomen, and extremities examination showed within normal limit. Liver and spleen were not palpable. The motoric strength and the physiological reflexes were normal. The extremities were warm with capillary refill times less than 3 seconds.

Baby 3 was assessed as suspicious of neonatal sepsis. The first complete blood count showed hemoglobin was 14.3g/dL, hematocrit was 42%, white blood cell count was 18,600/mm³ with 52% atypical lymphocytes, and platelet count was 21,000/mm³. Blood also taken for septic work up.

She was transferred to nursery ward for close monitoring of her illness. She got ampicillin sulbactam intravenous 100mg/kgbw/day divided into 2 doses, intravenous fluid of dextrose 10% 0.18 normal saline, and thermoregulation.

She continued to have fever approximately 39.8°C until the 16th day of life. That was the 4th day of illness. She did not complain of other symptoms and others physical examination also within normal limit. The complete blood count showed hemoglobin was 13.3 g/dL, hematocrit was 39%, white blood cell count was 14,000/mm³ with 39% atypical lymphocytes, and platelet count was 247,000/mm³

On the 7th day of illness, her body temperature became normal about 37.0°C - 37.3°C without uneventful recovery. She was an active baby. Blood culture result was negative for bacterial growth. The antibiotic were discontinued after 5 days treatment.

According to the history of baby 3 with sudden onset of fever, thrombocytopenia, and there was some children in her residential have been diagnosed got dengue virus infection, so we suspected baby 3 with dengue fever. The serology test of IgG and IgM anti dengue were examined. The result revealed an increased of anti dengue IgM and IgG with IgM titer higher than IgG, indicating a primary infection. The complete blood count hemoglobin was 12.1 g/dL, hematocrit was 33%, white blood cell count was 6,600/mm³ with 46% atypical lymphocyte, and platelet count was 190,000/mm³. Baby 3 was assessed as dengue fever.

Baby has been established for dengue infection, thus history of mother's illness was taken. A 29 years old mother, with the history of parturition: gravid 2, at 38/39 weeks gestation. Baby was born by spontaneous delivery with clear amniotic fluid. She had no experienced sudden febrile illness, headache, backache, myalgia, nausea, and vomiting before, during, and after delivery. Her blood pressure, temperature, pulse, and respiration rate were normal. Other physical examinations were normal. Mother was in healthy condition. Mother was also planned for laboratory confirmation of dengue infection. The complete blood count showed hemoglobin was 11.5g/dL, hematocrit was 34%, white blood cell count was 9,600/mm³, and platelet count was 345,000/mm³. The serology test IgG and IgM anti dengue were negative indicating there was no evidence of dengue infection in mother 3.

on 8th day of baby's illness, fever was improved. The vital sign was stable. There was no rash and no hemodynamic instability. She was breastfed properly without vomiting. The intravenous fluid therapy was stopped. The full blood count was taken every day until the 9th day of fever, when she was discharged in a good condition. Her serial blood examination and laboratory tests for dengue diagnostics were as shown in Table 3. In case 3, there was evidence of baby suffered of dengue virus infection but no evidence of mother. So baby 3 was having an acquired neonatal dengue infection.

Table 3. Temperature and serial complete blood counts of Baby 3

	3 rd day fever	4 ^d day fever	6 th day fever	7 th day fever	8 th day fever	9 th day fever
Baby						
40 °C						
39.5 °C						
39 °C						
38 °C						
37 °C						
36.5 °C						
36 °C						
White blood cell (mm ⁻³)	18.600	14.000	8.900	6.600	6.000	9.800
Neutrophils (%)	38	45	41	31	17	19
Lymphocytes (%)	52	39	44	46	59	63
Platelets (103/mm ³)	21	247	216	190	150	203
Haemoglobin (g/dL)	14.3	13.3	12.9	12.1	12	12.2
Haematocrit (%)	42	39	35	33	33	45
IgM				Positive		

RESUME OF CASES

There were 3 babies with 3 days old and 14 days old, came with fever as the main complaint, were accompanied with poor feeding, and only Baby 1 had evidence of jaundice. The fever was sudden onset and persisted. There were no complaint of dyspnea, cough, diarrhea, and seizure. The Baby 1 and 3 was born by spontaneous delivery whereas Baby 2 by cesarean section. All babies belonged to term infants, had good Apgar Score, no resuscitation was required, and appropriate body weight

All babies were alert, fussy, with stable vital signs, no history of hemodynamic instability. Physical examinations were normal, except Baby 1 with Kramer I-II.

All babies were initially assessed as suspicious of neonatal sepsis, where Baby 1 also developed neonatal jaundice along with a suspicion of TORCH infection. Accordingly all were treated with ampicillin sulbactam 100mg/kg/bw/day divided into 2 doses, fluid maintenance and nutrition with oral feeding also intravenous dextrose 10% 0.18 normal saline. They were also put on thermoregulation.

Complete blood count revealed thrombocytopenia in all babies, without leucopenia. There was no hemoconcentration more than 20% in all patients.

Mother's clinical manifestation varied. Mother 1 had no fever but only complaint of joint and retroorbital pain, also myalgia at parturition which became moderate. Mother 2 complained of fever, headache, backache, myalgia, nausea, and vomiting for 2 days before parturition. Whereas, Mother 3 did not complain of any symptoms. All mothers with stable vital sign, no signs of hemodynamic instability. Other systemic examinations were normal. The complete blood count revealed only thrombocytopenia in Mother 2 whereas others were within normal limits.

From history of illness Mother 1 and 2 stayed in an area which is known to have high transmission of dengue virus, where some have been diagnosed as dengue virus infection. Serology test of anti dengue IgM and IgG were positive in Mother 1 and 2 indicating secondary infection. Mother 1 had no complaint of fever, thus was diagnosed with dengue virus infection whereas Mother 2 with fever had dengue fever. Both mothers were in good condition.

Based on mother's history of illness in Baby 1 and 2, laboratory confirmation for dengue virus infection was taken. Immunoglobulin M was positive in both babies, indicating primary infection. The non structural 1 (NS1) antigen done on the 4th day of life in Baby 1 yielded a negative result. A polymerase C reaction (PCR) performed in Case 1 proved to be positive result for dengue type 3 (DEN-3).

Baby 3 was suspected for dengue fever because she developed sudden onset of fever, thrombocytopenia, and there was evidence of children with dengue infection in her neighborhood. Serology revealed positive IgM, indicating primary infection. However, mother's serology test resulted negative of anti dengue IgG and IgM. Therefore unlikely that the mother had a dengue infection at the same time. Table 4 showed the resume of all cases.

Table 4. Resume of Cases

CASE	BABY				MOTHER			
	Day of life	Onset of illness	Clinical findings	Laboratory	Dengue diagnostic test	Onset of illness	Clinical findings	Laboratory investigations and dengue diagnostic tests
1	3	1	Fever, poor feeding, jaundice	Thrombocytopenia	IgM+, PCR+, DEN-3	few hours before parturition	arthralgia, myalgia, and headache	PCR+ for DEN-3, IgG/IgM+ with higher IgG titer, secondary infection
2	3	2	Fever, poor feeding	Thrombocytopenia	IgM+	4 days before parturition	Fever, headache, myalgia, nausea, vomiting	Thrombocytopenia, IgG/IgM+ with higher IgG titer, secondary infection
3	14	11	Fever, poor feeding, vomiting	Thrombocytopenia	IgM+	No symptoms or signs	No symptoms or signs	Normal CBC, no evidence of serology

CBC: complete blood count, DEN: dengue virus, IgG: immunoglobulin G, IgM: immunoglobulin M, PCR: polymerase C reaction

DISCUSSION

There were 3 babies of 3 days old and 14 days old, came with sudden persisted fever as the main complaint, were accompanied with poor feeding, and only Baby 1 with jaundice. The fever was sudden onset and persisted. There were no complaint of dyspnea, cough, diarrhea, and seizure. Baby 1 and 3 were uneventfully born at term by spontaneous delivery whereas Baby 2 by cesarean section. All babies with term infant, good Apgar score, no history of premature rupture of membrane, and appropriate body weight.

Fever is defined as a core body temperature greater than 38°C in infants younger than 28 days. Fever is an extremely common pediatric presentation and has many different causes. A thorough history and clinical examination is essential in the evaluation of febrile infants. Detailed history is very important and can provide clues to the specific etiology of the fever. Questions should be asked about changes in feeding patterns, irritability, activity levels and other changes in behaviour. The birth history is also very significant in an infant presenting with fever.⁷

The most common etiology of fever in neonate is viral and bacterial infection. Viral infection including varicella, enteroviruses, influenza virus, respiratory syncytial virus. Bacteria that cause significant infection include Group B streptococcus (GBS), Escherichia coli and Listeria monocytogenes. The common sources of serious bacterial infections are urinary tract infections, bacteremia, osteomyelitis, cellulitis, bacterial gastroenteritis, meningitis, and pneumonia. Infected agent in neonate is also associated with risk of vertically transmitted infection, caused by positive group B streptococcus status without appropriate prophylaxis, maternal sexually transmitted, and TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus). Infected condition also associated with mother risk factor such as prolonged rupture of membranes, fever, and disease of mother.^{7,8,9}

All babies without complain of dyspnea, diarrhea, and seizure. Thus cause of infection by respiratory syncytial virus, adenovirus, and enterovirus could be

excluded. All mothers without history of premature rupture of membranes, clear amniotic fluid, no history of sexual transmitted infection, also without any infected disease. Thus no risk factor of vertically transmitted. The common sources of serious bacterial infections such as osteomyelitis, cellulitis, bacterial gastroenteritis, meningitis, and pneumonia could be excluded.

All babies were alert and fussy, with increased axillary temperature with normal other vital signs, no history of hemodynamic instability. Physical examinations revealed skin icteric with Kramer I-II of baby 1 whereas other baby's physical examinations of head, thorax, abdomen, and extremities were normal. Also perfusion was normal.

The physical examinations should including vital signs, skin colour, level of alertness, exanthems and hydration status. Atoxic neonate may present with irritability, inconsolability, poor tone, decreased activity, lethargy, poor perfusion and abnormal vital signs.^{7,10}

According to history taking and physical examination, all babies were assessed as suspicious of neonatal sepsis, because of temperature irregularity with fever and feeding problem, whereas Baby 1 associated with neonatal jaundice and suspected of TORCH infection.

Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life, can be classified into early and late onset sepsis that relative distinct syndromes based on the age of presentation. Early onset sepsis presents in the first 3 until 5 days of life usually multisystem fulminant illness with prominent respiratory symptoms while late onset sepsis may occur as early as 5 days of age, more insidious but can be fulminant, and usually not associated with early obstetric complications. Typically, the infant has acquired the organism during antepartum or intrapartum period from maternal genital tract.^{7,9,10}

Clinical signs and symptoms of sepsis are nonspecific, and the differential diagnosis is broad. Some signs are subtle or insidious, and therefore a high index of suspicion is required to identify and evaluate infected neonates. Clinical sign and

symptoms most often include change in behavior, feeding problems, focal infection, change in skin, and temperature irregularity can be hypothermia or hyperthermia that hyperthermia is more common in fullterm infants beyond the first 24 hours of life and if viral agent are involved. Some nonbacterial infection such as disseminated virus can be indistinguishable from bacterial sepsis and should be considered in the differential diagnosis, especially if infant has fever.^{7,8}

All babies got intravenous ampicillin sulbactam 100mg/kgbw/day divided into 2 doses after the usual septic workout such as blood culture and check for C-reactive protein. All babies got ampicillin until 5 days treatment. Besides intravenous fluid of dextrose 10% 0.18 normal saline was added, the babies were put on thermoregulation.

Empiric antibiotic therapy often begun before a definite causative agent is identified. The antibiotic usually ampicillin 100mg/kgbw/day divided into 2 doses. Ampicillin was selected for this case because 35-40% sepsis in neonate were suspected gram positive infection. The empirical regimen covers the most commonly encountered microorganism and has proved to be efficacious over the years. Also in neonate with clinically septic the supportive therapy such as intravenous fluid and thermoregulation was commenced.⁷

One of the clinical manifestation of neonatal sepsis is jaundice. Neonatal jaundice is the yellowish discoloration of the skin and or sclera of newborn infants caused by tissue deposition of bilirubin, seen when total bilirubin more than 5mg/dL. Icterus neonatorum can be physiologic or pathologic. Physiological icteric is mild, affects nearly all newborns, bilirubin level peak at 5 to 6mg/dL at 72 to 96 hours of age, and do not exceed 17 to 18mg/dL. It is clinically useful to classify jaundice with Kramer's rules associated to bilirubin level.¹⁰

Baby 1 looked jaundice on the 3rd day of life, with total bilirubin 5.5mg/dL which increased to 12mg/dL on the 5th day of life. On the 7th day of life, the icteric decreased. Thus hyperbilirubinemia in Baby 1 was physiological.

From serial complete blood count revealed thrombocytopenia in all babies without leukopenia or leukocytosis. Thrombocytopenia occur be in conformity with

improved fever. Although platelet was 18,000/mm³ in Baby 2 and 21,000/mm³ in Baby 3, there were no signs of bleeding such as petechie or hematin also platelet increased on the following day, transfusion of thrombocyte concentrate was not commenced. There was no hemoconcentration more than 20%. C-reactive protein was normal, and blood culture without bacterial growth. Thus the suspicious of neonatal sepsis could be excluded.

From mother's history of illness in Mother 1 and 2 stayed in an area some people were diagnosed as dengue infection, laboratory confirmation for dengue virus infection was taken. Serology test of anti dengue IgM and IgG were performed, and result were positive. Immunoglobulin M was positive in both babies. Whereas Baby 3 was suspected with dengue fever because sudden onset of fever, trombositopenia, and there was some children in her residential have been diagnosed with dengue infection. Laboratory revealed IgM was positive, but mother without evidence of dengue infection. So, all babies was diagnosed as dengue fever.

Dengue viruses are members of the family *Flaviviridae* and are of 4 serotypes (DEN-1, DEN-2, DEN-3, DEN-4). This mosquito-borne infection can be asymptomatic or lead to an undifferentiated fever (UF), dengue fever (DF) or dengue hemorrhagic fever (DHF) with plasma leakage, which possibly can develop into hypovolemic shock dengue shock syndrome (DSS).^{2,4}

From anamnesis and history of illness and laboratory result we diagnosed Baby 1 and 2 as well as their mothers as dengue infection. It has assumed that dengue infection was develop on the vertically transmitted because develop on the 3rd day of life. On the contrary baby 3 with evidence of sudden and persistent fever on the 11th day alone with thrombocytopenia, besides evidence of dengue virus infection among children in the neighborhood, we suspected that Baby 3 could have acquired dengue fever infection post natally.

Dengue infection in neonate can be transmitted vertically from infected mother and acquired infection. In our case, Baby 1 and 2 were hypothesized as vertical infection from infected mother was based on:^{11,12,13}

1. Confirmed maternal infection close to delivery time and mother was established having dengue infection
2. 3 until 5-days incubation period
3. Endemic area of dengue

Whereas Baby 3 was an acquired dengue fever infection because

1. Confirmed that mother without evidence of dengue infection
2. Onset fever when 11 days old
3. Endemic area of dengue

Incubation period of dengue virus infection is 3 until 7 days. We compared our case to the series of cases from other case report involving newborns and we found that the incubation period were similar. Time interval between the beginning of fever in the pregnant women and newborn in that cases of dengue infection vertical transmitted ranged between 1 to 13 days (mean time 7 days, onset of fever between mother to baby), which is similar to case 1 and 2. Although onset of fever of baby 3 was in 11th day of life, there was no evidence of vertical transmitted.^{11,14,15}

The period time of disease takes to develop in newborns usually between 5th to 13th day of life that is after hospital discharge. There might be cases of vertical infection that are not registered or diagnosed.^{6,15}

There were two mechanisms of dengue virus vertical transmitted related illness could be postulated:^{4,11,13,15}

1. Maternal infection during pregnancy may result in hematogenous spread of the virus to the placenta and subsequent passage to the fetus.
2. Maternal viremia during labour could result in viral transmission and infection of the fetus or the newborn because of blood exchange during the delivery process.

All babies came with complaint of sudden and persisted fever at 2nd, 3rd and 14th day of life, average of 38.7^oc-40^oc with poor feeding. Fever was improved between 3 until 5 day of illness. Only Baby 1 was complained of icteric.

Thrombocytopenia was found in all babies. Mother 1 was diagnosed as dengue virus infection that without fever, whereas Mother 2 with dengue fever. Mother 2 with thrombocytopenia ($126.000/\text{mm}^3$) but none of them with leucopenia.

Dengue fever in the newborn is characterized by a temperature of 38°C until 39°C . Non specific signs may present as poor sucking, irritability, or pallor. The symptom were present for 3 until 5 days, with an uneventful recovery in all cases. The disappearance of fever correlates with the disappearance of viremia.^{12,16}

Pregnant women and newborn symptoms vary among the case reports published in the literature; however, in general, the most common symptoms include fever and thrombocytopenia. In our case, babies reported symptoms fever, poor feeding, and thrombocytopenia. Table 5 show cases report with clinical symptoms in pregnant women and newborn.¹² Complication of bleeding may occur in both mothers and infants. The presence of wounds or trauma due to birth coinciding with a period of marked thrombocytopenia, abnormal platelet function and coagulation abnormalities were risk of severe uncontrollable hemorrhage.^{15,16}

Table 5. Cases report with clinical symptoms in pregnant women and new born

Author	Country	Number of cases	Pregnant women's symptoms	Newborn's symptoms
Phongsamart et al	Thailand	3	Erythematous rash and thrombocytopenia	Fever, petechiae, and hepatomegaly
Sirinavin et al	Thailand	2	Thrombocytopenia and elevated liver enzymes	Fever, thrombocytopenia, elevated liver enzymes, bleeding, and rash
Petdachai et al	Thailand	1	Fever and thrombocytopenia	Thrombocytopenia, leucopenia, petechiae, and hepatomegaly
Janjindamai et al	Thailand	1	Fever	Thrombocytopenia and elevated liver enzymes
Choudhry et al	India	4	No information	Fever, lethargy, shock, and thrombocytopenia
Witayathaworn	Thailand	1	Thrombocytopenia	Fever, thrombocytopenia,

wong et al			and pleural effusion	and pleural effusion
Restrepo et al	Colombia	22	No report	Preterm delivery, fetal malformations, and low birth weight
Fatimil et al	Bangladesh	1	Bleeding and pleural effusion	Fever and thrombocytopenia
Chotigeal et al	Thailand	2	Postpartum hemorrhage	Thrombocytopenia and pleural effusion

Source: Maroun SL, Marliere RC, Barcellus RC, Barbosa CN, Ramos JR, Moreira ME. Case report: vertical dengue infection. J Pediatr. 2008; 84:556-9.

On physical examination, all babies and mother without flushed skin or erythematous rash, except Baby 1 with icteric. The liver and spleen were not palpable, also no sign of plasma leakage and bleeding. Skin perfusion was normal.

Flushed skin or erythematous rash in the face also occurred while febrile, and the rash subsequently become generalized or localized in the arms and legs. Skin eruptions may be more common in primary infections. The rash may be present in face, neck, or chest during febrile period. Less frequent than rash but not rare are mild hemorrhagic manifestations such as petechiae, epistaxis, gingival hemorrhage, gastrointestinal hemorrhage, and microscopic hematuria. Hemorrhage is more commonly associated with a platelet count below 50,000/mm³, although hemorrhage does not necessarily occur with a low platelet count. Hepatomegaly was present at the onset of symptoms in two of the eight dengue cases from previous case report, with mild elevations of hepatic enzymes, normal bilirubin level.^{14,12,16}

From CBC revealed thrombocytopenia (<150,000/mm³) in all babies at 3rd to 5th day of fever that time of fever defervescent but not in baby 3. There were no hemoconcentration more than 20% and leukopenia (<4,000/mm³) in all cases.

Clinical manifestation of dengue infection vary among neonate, infant, and children, where in neonate the manifestation of fever and thrombocytopenia were 82% of cases, rash was 12% of cases, pleural effusion was 24% of cases, liver enlarged was 65% of cases, had at least

some evidence of bleeding, but none required transfusion despite some very low platelet counts. Whereas the clinical manifestation in infant or children more severe because transplacental maternal antibodies are felt to be protective typically about 6 month of age. After that, however, the lower titers may in fact result in immunological enhancement and predispose the infant to DHF or dengue shock syndrome.^{16,17}

The laboratory evaluation of both mother and newborn with a suspected case of dengue must involve a variety of diagnostic tests, including specific tests for dengue. A complete blood cell count should be ordered for evaluation of the WBC count, hemoglobin and hematocrit levels, and platelet count. Serial CBC are needed during the first days of illness to evaluate the disease progression, especially for hemoconcentration, an important marker of increased capillary permeability.^{13,16,17}

Serology tests of anti dengue IgM were positive in all babies, indicating primary infection. Serology test of mothers revealed positive result of anti dengue IgG and IgM with higher IgG in both Mother 1 and 2, indicating secondary infection, but negative result in Mother 3. The non structural 1 (NS1) antigen taken on 4th day old of life in baby 1 revealed negative result. Only case 1 (baby and mother) was performed PCR with positive result for dengue type 3. Thus, these babies were absolutely uninfected by dengue virus.

Serological diagnosis depends on the presence of anti dengue IgM antibody or a rise in IgG antibody titer (acute and convalescent phase). Immunoglobulin M antibody becomes detectable during the acute phase of illness, and 90% of infected persons are IgM positive by the 6th day after the onset of symptoms. Immunoglobulin M antibody titer is increase higher than IgG in primary infection, but in secondary infection, IgG antibodytiter higher than IgM. Specimens collected less than 6 days after the onset of symptoms will have a variable percentage of samples without IgM antibodies. For the reason, negative result in samples obtained during the acute period are considered indeterminate, and a second sample during the convalescent period (6-21 days after onset),

should be requested. Negative result in samples were obtained in this period may be considered true negative. The presence of IgM anti dengue antibody is considered as only probable evidence of recent dengue infection because it may be detectable for about 60 days.^{11,12,18} The humoral immune response during first and second infection shown by Figure 1.⁶

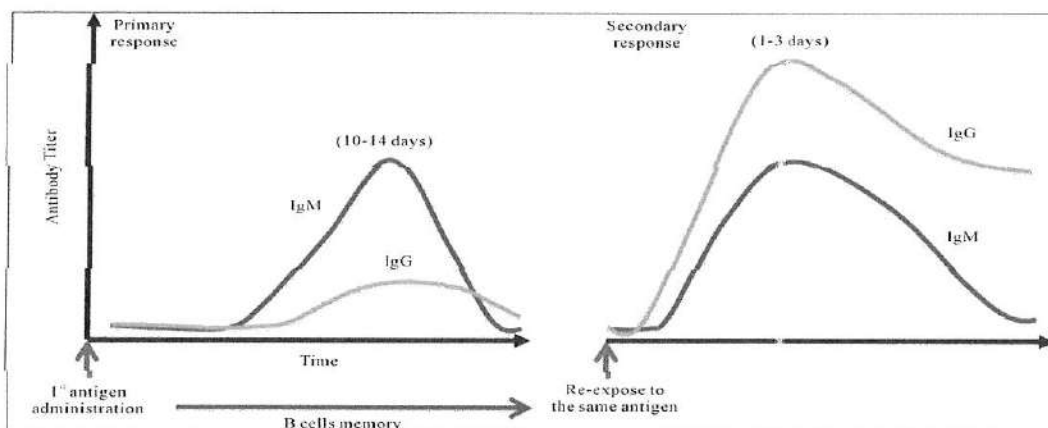


Figure 1. Humoral immune response during first and second infection
 Source: Tan PC, Rajasingam G, Devi S, Omar SZ. Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. *Obstet Gynecol.* 2008;111:1111-7.

Diagnostic sensitivity of NS1 detection in the febrile phase can exceed 90%. Real time reverse transcription-PCR (RT-PCR) methods are sensitive to classified serotype of dengue because dengue serotypes may play a role in the severity of disease. In vertical transmission, we can find the same dengue serotypes from both of mother and infant.^{16,18,}

Dengue serotype distribution in Surabaya is changed over year. In 2008-2009, the four serotypes are dominated by DEN-2 with 52%, 20% of DEN-1, 16% of DEN-3, and 12% of DEN-4. Dengue virus serotype distribution is known to be dynamic and serotype predominance may change through time.¹⁹ In 2012 the predominance serotype is DEN-1 with 60.56%.²⁰ In Java, the major serotype is DEN-3. The laboratory diagnosis of DENV serotype should be routinely performed to follow the dynamic of dengue disease.²¹

Anti dengue Immunoglobulin G is a dominant isotype immunoglobulin and only Ig across placenta. There was 4 subtype of IgG, such as IgG1, IgG2, IgG3, and IgG4, each transfer proportional. There was slightly IgG synthesis by fetus thus active transport of maternal IgG through placenta, although still unclear mechanism. Fetus IgG is influence by gestation week, in 40 week gestation fetus IgG compared with maternal IgG. ^{22,23} The correlation between maternal antibody and risk of disease shown by Figure 2.²³

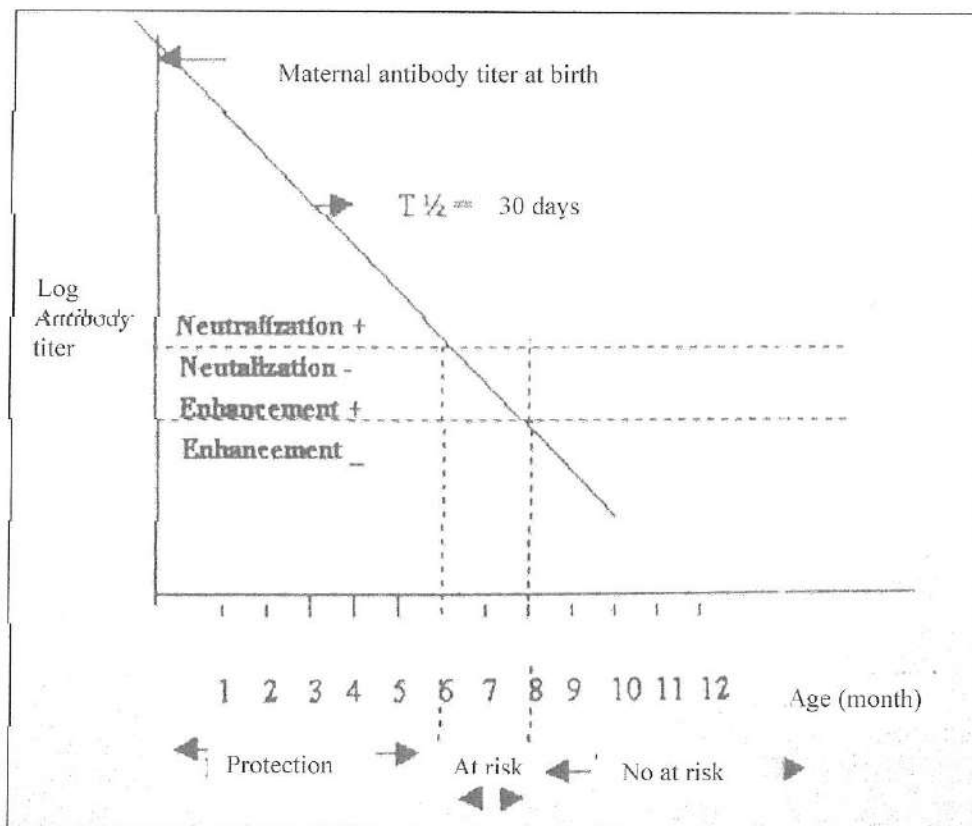


Figure 2. Correlation between maternal antibody and risk of disease
 Source: Klicks SC, Nimmanitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue haemorrhagic fever in infants. *Am J Trop Med Hyg.* 1988;38:411-9.

When baby born, the anti dengue antibody titers were similar to maternal. Antibody and protect baby from dengue virus. Maternal antibody titer will decrease

until unprotected antibody named infection-enhancing antibody (IIEA). If baby infected in this condition, mild first dengue infection could be dengue hemorrhagic fever or dengue shock syndrome. Maternal IgG usually not found in baby more than 8 month. Some authors have reported that severe dengue affects the newborn only when the mother's symptoms occur close to term or delivery time because the mother has no time to produce protective antibodies in mother with primary infection.^{16,17,22,23}

In this case our patients did not see any sign of bleeding in both mother and infant event though here was decrease of the thrombocyte. The manifestation and natural history of dengue virus infection in our case were similar with most cases.²⁴

Hemorrhage does not necessarily occur with a low platelet count. The manifestation was not severe because mother with secondary infection thus there was maternal antibody transferred to neonate. Although the natural history of dengue in neonate similar in infant and children but may be influence by mother antibody. The natural history of dengue virus infection showed in Figure 3.²⁵

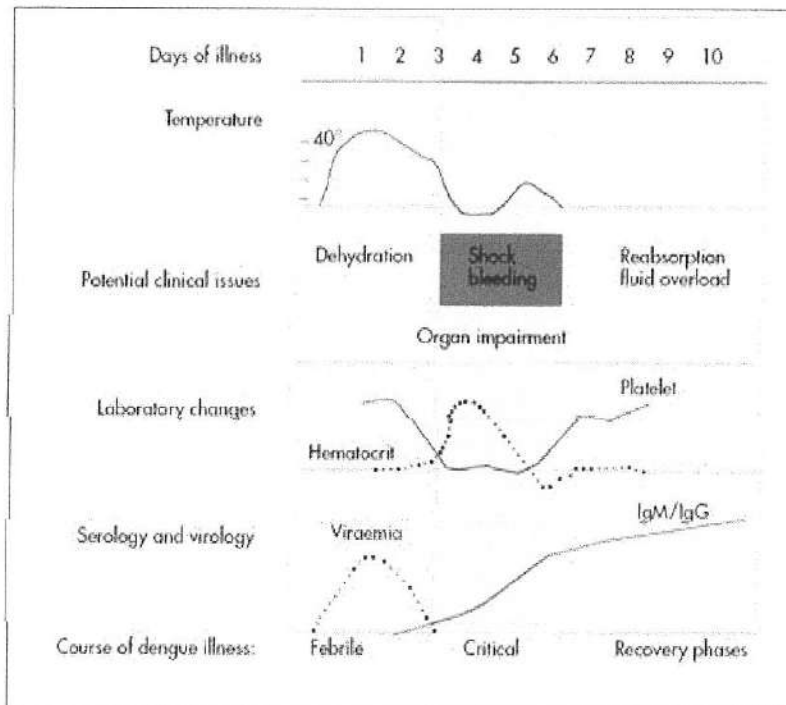


Figure 3. Natural history of dengue virus infection
 Source: Verhagen LM, Groot R. Dengue in children. J Infect. 2014; 69:77-86.

All babies shown an uneventful recovery. They were discharged on good condition. Prognosis of these babies was good because there was no any complication of bleeding and other severe condition.

Awareness and early recognition of perinatal dengue together with the availability of a better laboratory test based on serological test for early laboratory confirmation of acute dengue, but clinical features combined with CBC and platelet counts at the appropriate time provide quicker suggestive dengue infection will contribute to early appropriate management and significant reduction of maternal and infant mortality. Prognosis was good if there were no complication in the baby.^{6,15,24}

A high level of awareness, early diagnosis, and management of vertical transmission to newborns from mothers with dengue virus infection are very important, especially in endemic areas such as Indonesia.¹

SUMMARY

Three cases of dengue virus infection in neonate have been reported. They were 3 and 14 days old, came with sudden onset and persistent fever as the main complaint, doing with poor feeding, and jaundice in Baby 1. There were no evidence of dyspnea, cough, diarrhea, and seizure. The Baby 1 and 3 was born by spontaneous delivery whereas Baby 2 by cesarean section. All babies were uneventfully born at term, did not required resuscitation, and had appropriate body weight.

All babies were alert with stable vital sign, no history of hemodynamic instability. Physical examinations were normal, except Baby 1 with Kramer I-II. Initially, all babies were assessed as suspicious of neonatal sepsis, along with neonatal jaundice in Baby 1. All babies were treated with ampicillin sulbactam, maintenance fluid, and oral feeding along with thermoregulation. All babies had thrombocytopenia without evidence of leukopenia or hemoconcentration more than 20%

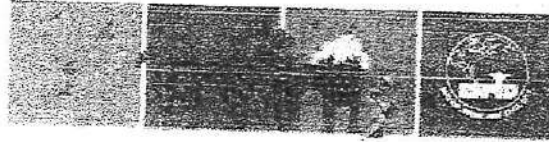
Mother is clinical manifestations varied from asymptomatic to fever, joint and retroorbital pain, myalgia, headache, backache, nausea, and vomiting for 4 days before parturition and during parturition. Vital sign and hemodynamic were stable. Thrombocytopenia was evident only in Mother 2.

Being residence of an dengue endemic area, serology proven positive IgG along with anti dengue IgM in Mother 1 ad 2 indicating have a secondary infection in. In their off springs, a primary infection, were all evidence that suggested vertical transmission of dengue in case 1 and 2. Only case 1 had a PCR performed resulting in a DEN-3. In the contrary, a negative serology test of the Mother 3 along with a primary infection of Baby 3 led to conclusion of acquired dengue virus infection after birth in case 3. All babies shown an uneventful recovery. They were discharged on good condition.

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