# Outcome of Neonates Exposed to Active Pulmonary Tuberculosis

Suchaorn Saengnipanthkul MD*,
Junya Jirapradittha MD**, Pakaphan Kiatchoosakun MD**

** Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
*** Division of Neonatology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

***Objective:*** *To determine the incidence of tuberculosis infection and disease in neonates exposed to an active pulmonary tuberculosis patient in a nursery and maternity ward.*
***Material and Method:*** *Descriptive cohort study was carried out in Srinagarind Hospital, Khon Kaen University, North-East Thailand. A smear positive pulmonary tuberculosis mother with productive cough was diagnosed on the fifth day of admission. The authors urged parents of all exposed neonates to accept isoniazid (INH) prophylaxis for their infants for six months. All neonates underwent chest x ray (AP, lateral view) and tuberculin skin test on the 24 months follow-up.*
***Results:*** *The 48 neonates were identified as exposed. The age of follow-up ranged from 30 to 32 months. Only three were lost to follow-up. Of the remaining 45 neonates, six refused to take INH prophylaxis. Complete six months of INH prophylaxis were observed in 27 (60%) of 39 contacts. Tuberculin skin tests (TST) were performed in all of 45 contacts. No cases were positive for TST. Abnormal chest radiographies were found in nine of INH group, three patients had hilar lymphadenopathy and six had pneumonia. The repeat chest x ray, two weeks later, was normal in all cases. After 30 to 32 months follow-up, none of the 39 neonates who received INH prophylaxis or the six neonates progressed to have active tuberculosis.*
***Conclusion:*** *In exposed neonate identified as the high-risk group, appropriate INH prophylaxis, and long-term follow-up, especially in the first-2 years, seemed to be effective in preventing the development of active tuberculosis.*

***Keywords:*** *Neonatal exposure, Pulmonary tuberculosis, Isoniazid prophylaxis, Outcome*

***J Med Assoc Thai 2012; 95 (6): 756-60***
***Full text. e-Journal:*** *http://jmat.mat.or.th*

Tuberculosis (TB) is one of the ten leading causes of death in children. More than 75% of newly diagnosed TB in children is in the 22-high TB-burden countries, including Thailand[1]. Infants were at highest risk with TB disease developing in 50%. The risk decreased to 20% in the second year of life[2]. Primary infection before two years of age frequently progressed to miliary disease, pulmonary disease (Ghon focus, lymph node and bronchial disease), and tuberculous meningitis within the first 12 months without significant symptoms.

A neonate born to a pregnant woman found to have pulmonary TB shortly before delivery is more likely to become infected. Center of Disease Control and Prevention, Division of Tuberculosis Elimination recommends that neonate should receive six months of isoniazid preventive therapy, followed by BCG immunization[3]. The Thoracic Society of Thailand and Department of Communicable Disease Control, Ministry of Public Health recommends for isoniazid prophylaxis to these neonates immediately and TST at three months of age. At that time, the medication can be discontinued if the test is negative or continued for six months if TST is positive. Breastfeeding can be safely continued during this period[3,4].

***Correspondence to:***
*Saengnipanthkul S, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.*
*Phone: 088-510-1031, Fax: 043-363-012*
*E-mail: Suchaorn@hotmail.com*

**The index patient history**

The nursery and maternity ward at Srinagarind Hospital has three different types of rooms. The first was an open ward-style room that contains 20 beds with positive pressure ventilation and air recirculation system. The second was two single rooms with the same air recirculation system. The last was the exception of four single rooms, each room isolated from other areas with independent positive pressure ventilation system.

On December 26, 2008, a 20-year-old human immunodeficiency virus-seronegative went into labor at 36 weeks gestation and delivered a male neonate,

weighing 2,350 grams. She was evaluated for a productive cough of four-week duration and recent intermittent low-grade fever. A chest radiography showed bilateral diffused fine reticulonodular infiltration with right pleural effusion. Sputum smear obtained on the fifth day following admission was reported as positive for acid-fast bacilli. On December 31, pulmonary TB was diagnosed. She was moved to a single room and started on anti-tuberculous therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide. The cultures of two sputum samples were identified later as *Mycobacterium tuberculosis* and susceptible to all antimicrobials tested.

The baby was moved to the sick newborn ward to isolation. At 32 weeks' gestation, his mother was experiencing productive cough, fever, and poor weight gain. The baby underwent laboratory investigations to rule out congenital tuberculosis, even if he had no signs of active TB disease. His chest radiograph was normal, three consecutive days gastric aspirates were negative for TB. Lumbar puncture and urine culture were normal. At that time, the placenta was not available for placental histopathology and TB culture. Isoniazid 5 mg/kg/day was given as chemoprophylaxis with a supplementation of Vitamin B6 for nine months.

After the smear positive pulmonary TB mother was diagnosed, the Srinagarind Hospital Committee, including hospital infection control authority, experts from the pediatric department (neonatologist, infectious disease specialist and pulmonologist), and public health authority, immediately defined the protocol for investigation and preventive treatment for all potentially exposed cases. The committee first prioritized neonates and mothers, who had been in the nursery between December 26 and 31, 2008 as at possible risk of contracting tuberculosis. Beside the neonates, children aged less than five years and their guardians were evaluated. All neonates received BCG vaccination within 24 hrs after admission. Mothers were notified by mailing the certified letters or telephone calls to inform the risk and encouraged them to receive INH prophylaxis for their infants for six months and evaluated by a neonatologists at three months, six months, and one-year follow-up visits.

The main purpose of the present study was to determine the long-term incidence of tuberculous infection and disease in neonates who contacted with active pulmonary tuberculosis patient in nursery and maternity ward.

**Material and Method**

A prospective study was conducted between January 2009 and September 2011 at Srinagarind Hospital, a tertiary care and referral center in the North-East of Thailand. To identify high-risk neonates, hospital records for patients in the nursery and maternity ward who were potentially exposed to the index patient, during the infectious period, were reviewed by the committee. The investigation included 48 infants, 47 mothers (1 was twins), and three children aged under five years who visited their siblings in the maternity ward at that time.

Each parent was contacted by phone or letter to remind the situation in the past and the two years follow-up investigations began. Each child was subjected to an initial clinical examination, TST (the result was read after 48 to 72 hours, an area of induration $\geq$ 10 mm in transverse diameter after TST was regarded as significantly positive), and antero-posterior and lateral chest radiographs. The tests were done in all children with written informed consent after counseling the parents. In case of inconvenience to visit at Srinagarind Hospital, the doctor of a regional hospital was asked to assist in following-up, TST, and chest x ray imaging the exposed infants.

Children were classified as non-infected, infected, or disease. Non-infected child was asymptomatic, had a non-significant TST (< 10 mm), normal chest radiograph. A child with a TST $\geq$ 10 mm who was asymptomatic, had a normal chest radiography was regarded as having infection and not disease (Latent tuberculosis infection, LTBI). Diseased (tuberculosis disease) were diagnosed in symptomatic child with at least two or more positive findings, including abnormal chest radiograph (well-defined hilar or mediastinal adenopathy, military TB, pleural effusion or endobronchial TB), a TST more than 10 mm, history of exposed to pulmonary TB case, and those with a positive culture for *M. tuberculosis* from any source.

Information obtained from the subjects and investigations were recorded on case record forms. Data were analyzed by descriptive statistics, mean, and proportion.

The present study protocol was reviewed and approved by the Khon Kaen University Ethics Committee for Human research based on the Declaration of Helsinki and the ICH Good Clinical practice guideline, reference number HE541121. Written informed consent was obtained from the parents or guardians for participation in the present study.

## Results

### *The index patient, her son and household contacts*

The treatment was started on December 31. The patient improved symptomatically after one week of therapy. She returned home to continue treatment as outpatient. The patient isolated from her family for two months and breastfeeding was not allowed for two weeks. The patient's smear had converted to negative at one-month visit. She received a full course of anti-tuberculous drugs, consisting of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months of isoniazid and rifampicin without complication. Subsequently, she had successfully recovered from lung lesions, assessed by radiology at six months and one-year follow-up visits. No source for the index case was found in her community.

The baby lived with his father and grandmother. INH preventive treatment was given for nine months. The clinical evaluations at three months, six months, nine months, and one year follow-up visits were normal. At two years follow-up visit, he had a normal growth pattern and BCG scar was present. Chest radiograph (antero-posterior and lateral view) were normal and TST reaction was less than 10 mm.

Seven household contacts lived in the same house with the index case during the infectious period (all older than 5 years of age). All were evaluated by the local health department, including three children. Each contact person had a normal chest x ray. TST results of three children were all negative.

### *Evaluation of the potentially exposed neonates*

The committee categorized 48 neonates as being at high risk of infection. At the initial evaluation, 46 neonates (95.8%) were seen. Of these, 41 received INH prophylaxis. Fig. 1 shows the follow-up visits.

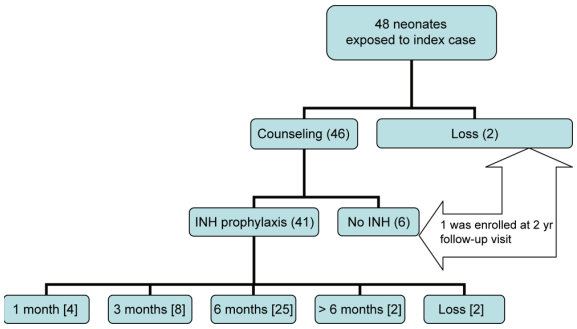


**Fig. 1** Flow diagram to summarize the follow-up visits

Three (6.2%) of 48 follow-up letters were returned as undeliverable on two years follow-up visit. Evaluation showed the age of 45 neonates ranged from 30 to 32 months and the male:female ratio was 1.2:1. Chemoprophylaxis was successfully administered to 27 neonates (69.2%), 12 neonates did not receive adequate chemoprophylaxis, and six neonates did not receive INH (refused by parents). Investigation of neonates showed that the body weight ranged from 11 to 21 kg (mean 13.8 kg), the height ranged from 83 to 97 cm (mean 89.5 cm), and head circumference ranged from 47 to 51 cm (mean 48.7 cm) at 32 months of age. Absent BCG scar was detected in five of 45 neonates (11%) despite BCG-vaccination. The test results are summarized in Table 1.

The hilar adenopathy was present on chest radiography in three and pneumonia in six of nine children in INH prophylaxis group and one pneumonia in non-INH group. Repeated chest x rays, two weeks later, of all 10 children, were normal.

Forty-five high-risk infants were evaluated, and all of them had negative TST results. Table 1 summarizes the investigations. No cases of TB disease,

**Table 1.** The tests result at 2 years follow-up visit

| Group | Tuberculin skin test | | Chest x ray AP, lateral view | | | Not test |
|---|---|---|---|---|---|---|
| | ≥ 10 mm | < 10 mm | Normal | Hilar adenopathy | Pneumonia | |
| No INH [6] | 0 | 5 | 4 | 0 | 1 | 1 |
| INH [41] | 0 | 37 | 28 | 3 | 6 | 2 |
| 1 month [4] | 0 | 4 | 4 | 0 | 0 | 0 |
| 3 months [8] | 0 | 8 | 6 | 0 | 2 | 0 |
| 6 months [25] | 0 | 23 | 16 | 3 | 4 | 2 |
| More than 6 months [2] | 0 | 2 | 2 | 0 | 0 | 0 |
| Loss of follow up [2] | - | - | - | - | - | 2 |

LTBI, or unexplained illness in exposed neonates were reported in the subsequent 24 months.

## Discussion

Neonatal tuberculosis is associated with a high mortality rate[5]. In 1976, there was a report of two babies who were born in the same maternity ward, had developed military TB. A nurse aid at the nursery was diagnosed as smear positive pulmonary TB[6].

The present study showed that no infants were TST-positive at 2-year follow-up, which is consistent with other reports which have shown that transmission of *M. tuberculosis* to exposed neonates were not identified. Sen M and associates[7] reported the 124 neonates who received INH prophylaxis after being exposed to a physician with active pulmonary TB. The investigation did not identify any newly positive skin test results at three months-follow-up.

Nania JJ and associates[8] reported 146 neonates exposed smear negative pulmonary TB. No disease developed during 20 months-follow-up in the non-INH prophylactic infants.

However, in a study by Schaaf HS et al[9], a 30 months-follow-up of children < 5 years old in contact with MDR TB adult showed that 5% (2/41) of appropriate INH chemoprophylaxis group and 20% (13/64) of children did not develop TB during follow-up (odds ratio: 4.97).

The difficulty arises in defining "significant exposure" since multiple factors must be considered. The significant exposure is based on several variables known to affect transmission of TB disease, including the duration of exposure, the quantitative aerosolization of *M. tuberculosis*, the volume and ventilation characteristics of the nursery, individual contact characteristic, and pathogenicity of the isolated *M. tuberculosis*[5]. The risk of infection is greatest if the contact is close and prolonged such as the household contact.

Because the present and earlier studies suggest that very low incidence of new neonatal tuberculosis developed after exposure to an active pulmonary TB cases in the nursery or other healthcare settings, the recommendations of isoniazid prophylaxis will likely depend on the severity of disease in the index case and the level of exposure.

## Conclusion

From the present study and the few reported cases in the literature, the authors suggest that a neonate with significant exposure to an index case with high likelihood of transmitting infection, isoniazid prophylaxis is recommended if there are no contraindications. In addition, the high-risk neonate should be followed-up for at least two years.

## Potential conflicts of interest

None.

## References


1. World Health Organization. Global tuberculosis control-epidemiology, strategy, financing [Internet]. WHO report 2009 [cited 2010 Aug 9]. Available from: http://www.who.int/tb/publications/global_report/2009/en/index.html
2. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Respir Crit Care Med 2006; 173: 1078-90.
3. World Health Organization. Contact screening and management. Guidance for national tuberculosis programme on the management of tuberculosis in children. Geneva: WHO; 2006.
4. The Tuberculosis Control Association of Thailand, The Thoracic Society of Thailand, Department of Communicable Disease Control, Ministry of Public Health. National guideline for treatment of tuberculosis. 2nd ed. Bangkok: The Tuberculosis Control Association of Thailand; 2000.
5. Burk JR, Bahar D, Wolf FS, Greene J, Bailey WC. Nursery exposure of 528 newborns to a nurse with pulmonary tuberculosis. South Med J 1978; 71: 7-10.
6. Steiner P, Rao M, Victoria MS, Rudolph N, Buynoski G. Miliary tuberculosis in two infants after nursery exposure: epidemiologic, clinical, and laboratory findings. Am Rev Respir Dis 1976; 113: 267-71.
7. Sen M, Gregson D, Lewis J. Neonatal exposure to active pulmonary tuberculosis in a health care professional. CMAJ 2005; 172: 1453-6.
8. Nania JJ, Skinner J, Wilkerson K, Warkentin JV, Thayer V, Swift M, et al. Exposure to pulmonary tuberculosis in a neonatal intensive care unit: unique aspects of contact investigation and management of hospitalized neonates. Infect Control Hosp Epidemiol 2007; 28: 661-5.
9. Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics 2002; 109: 765-71.

## ผลลัพธ์ของทารกแรกเกิดที่สัมผัสผู้ป่วยวัณโรคปอดระยะแพร่เชื้อ

*สุชาอร แสงนิพันธ์กูล, จรรยา จิระประดิษฐา, ผกาพรรณ เกียรติชูสกุล*

***วัตถุประสงค์:*** *เพื่อศึกษาอุบัติการณ์ของการเกิดวัณโรคในทารกแรกเกิดที่สัมผัสผู้ป่วยวัณโรคปอดระยะแพร่เชื้อในหอผู้ป่วยมารดาหลังคลอดและทารกแรกเกิด ทั้งในกลุ่มที่ได้รับยา Isoniazid (INH) เพื่อป้องกันการติดเชื้อวัณโรค และกลุ่มที่ปฏิเสธการรับยา*

***วัสดุและวิธีการ:*** *การศึกษาแบบไปข้างหน้า ในทารกแรกเกิดที่มีโอกาสสัมผัสผู้ป่วยเป็นวัณโรคปอดระยะแพร่เชื้อ แต่ได้รับการวินิจฉัย 5 วันหลังคลอด บิดาและมารดาของทารกกลุ่มดังกล่าวได้รับคำแนะนำเพื่อให้ยา INH เป็นเวลา 6 เดือน รวมทั้งทำการทดสอบปฏิกิริยาทุเบอร์คุลิน และภาพถ่ายรังสีทรวงอกทั้งด้านหน้า และด้านข้าง เมื่ออายุครบ 24 เดือน*

***ผลการศึกษา:*** *ทารกที่สัมผัสผู้ป่วยวัณโรคทั้งสิ้น 48 ราย ส่วนใหญ่ติดตามการรักษาที่อายุ 30-32 เดือน มีเพียง 3 ราย ที่ไม่สามารถติดต่อได้ ผู้ปกครองของทารก 6 ราย จาก 45 ราย ปฏิเสธการรับยา INH มีทารก 27 ราย ที่ได้รับยา INH ครบ 6 เดือน คิดเป็นร้อยละ 60 ผลการทดสอบปฏิกิริยาทุเบอร์คุลินให้ผลลบทุกราย ในกลุ่มที่ได้รับยา INH พบความผิดปกติจากภาพถ่ายรังสีทรวงอก 9 ราย ได้แก่ hilar lymphadenopathy 3 ราย และ pneumonia 6 ราย ในกลุ่มที่ปฏิเสธการรับยาภาพถ่ายรังสีทรวงอกพบ pneumonia 1 ราย แต่ทั้ง 10 ราย ไม่พบความผิดปกติจากภาพถ่ายรังสีทรวงอกที่ถ่ายซ้ำอีก 2 สัปดาห์ต่อมา ผลการศึกษาครั้งนี้ไม่พบการติดเชื้อวัณโรคในเด็กทั้งกลุ่มที่ได้รับยา INH และปฏิเสธการรับยา*

***สรุป:*** *การให้ยา INH chemoprophylaxis รวมทั้งการให้คำแนะนำและติดตามอาการโดยเฉพาะช่วง 2 ปีแรกหลังสัมผัสโรค มีประโยชน์แก่ทารกและช่วยลดการเกิดวัณโรคในภายหลัง*