

Suspected transmission of tuberculosis in a maternity ward from a smear-positive nurse: preliminary results of clinical evaluations and testing of neonates potentially exposed, Rome, Italy, 1 January to 28 July 2011

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We report preventive measures adopted after tuberculosis (TB) transmission from a nurse to a newborn assessed in late July 2011. All exposed neonates born between January and July 2011 were clinically evaluated and tested by QuantiFERON TB gold in-tube; newborns testing positive were referred for prophylaxis. Of 1,340 newborns, 118 (9%) tested positive and no other active cases of TB were found. Active surveillance for TB will be continued over the next three years for all those exposed.

Case descriptions

Case one

On 18 July 2011, a case of pulmonary and extra-pulmonary (splenic) tuberculosis (TB) was diagnosed in a four-month old infant at the children's hospital 'Bambino Gesù' in Rome, Italy. The diagnosis was confirmed by microscopic and sputum culture. According to international guidelines for TB prevention [1], all household members (parents and siblings, and two close contacts who took care of the baby) were screened for TB. No active TB cases were found and only the mother had a positive tuberculin skin test (TST) but was QuantiFERON TB gold in-tube (QFT-IT) TB-negative, most likely due to Bacillus Calmette-Guérin (BCG)-vaccination as a child. Although they tested negative, the two siblings, both below five years of age, were referred for prophylaxis.

Case two

On 26 July, pulmonary TB was clinically diagnosed in a patient at 'Gemelli' hospital, Rome and hereafter microbiologically confirmed by sputum culture as *Mycobacterium tuberculosis*, sensitive to first-line drugs, at the National Institute for Infectious Diseases

L. Spallanzani, Rome. The patient, a nurse by profession, reported onset of night cough since the beginning of April 2011 and a mild asthenia that was attributed to the daily work and diet, as well as loss of 17 kg body weight (corresponding to almost 20% of the total weight). The loss of weight was interpreted as intentional since she had been on a low-calorie diet since February 2011. In June 2011, a sinusitis had been diagnosed and beclometasone aerosol prescribed.

As soon as the nurse was suspected as a case of TB, investigation of household members found her husband and son TST-positive. Furthermore, the husband had a history of exudative pleurisy in 2004. Pleural fluid and sputa had resulted negative for *M. tuberculosis* isolation by culture at that time; the husband had nevertheless undergone a full course of TB therapy, consisting of two months of quadruple therapy with isoniazid, rifampicin, ethambutol and pyrazinamide, followed by four month of double therapy with isoniazid and rifampicin with a supplementation of vitamin B over the whole six months. Subsequently, he had successfully recovered from lung lesions, as assessed by radiology, and in terms of clinical symptoms. Therefore he had been diagnosed with pleural TB based on clinical grounds. At that time, the nurse was not tested by TST since her husband was deemed not contagious.

Because the nurse had been working in the maternity ward, at the same university hospital where the child (case one) was born in March 2011, an epidemiological link between the two cases was suspected. DNA fingerprinting of the isolated and cultured samples of *M. tuberculosis* in the two cases confirmed the link.

Epidemiological background

Italy is a low TB prevalence country according to the World Health Organization (WHO) definition [2,3]. The annual incidence in Lazio (the region including Rome, 5.6 million inhabitants), taking into account under-reporting, has been estimated to be around 11/100,000 [4]. Only 30 cases in children under one year of age have been reported annually to the local health authorities and regional public health agency in the last five years (12/100,000) [5].

Very few nosocomial outbreaks involving newborns have been described to date [6-14]. Here we report a case of TB that occurred in a four-month old infant potentially linked to a nurse diagnosed with TB who worked in the maternity ward when the child was born.

Investigation of potentially exposed newborns

Immediately after diagnosis of pulmonary TB in the nurse working in the maternity ward, a task force, including public health authorities, hospital infection control authority, and experts from the paediatric and infectious disease reference centres, defined the protocol described below for epidemiological investigation and preventive treatment.

The exposed group was defined as all the newborns (n=1,738) who were cared for in the maternity ward from three months before symptoms onset in the nurse to two days after the nurse's last working day (i.e. from 1 January to 28 July, 2011). Parents were contacted by phone and by mail, and counselled about the potential risk of infection and invited for a clinical visit and a screening test for the child in three paediatric outpatient clinics located in three different hospitals in Rome.

The task force decided to use QFT-IT (Cellestis Limited, Carnegie, Victoria, Australia) to screen newborns for several reasons: first, previous outbreak investigations of maternal wards suggested a lower sensitivity to latent TB infection of TST in neonates than in adolescents or adults [6-8,15]; second, it has been suggested to be more accurate than TST in low- and middle-income countries on children [16]; and, third it does not require, as does the TST, a second visit to assess results, which may be problematic for such a large population. However, there are very few studies of QFT-IT accuracy in newborns [16,17]. In any case, all children were tested by QFT-IT from 18 August. Since birth and potential exposure to *M. tuberculosis* were concurrent, and exposure was limited to one to two days during the hospitalisation in most cases, in the neonates below 12 weeks of age tested at the screening in August, a second QFT-IT and clinical evaluation were planned at the completion of three months of age. This is in agreement with guidelines that indicate an evaluation of contacts after the completion of three months from exposure.

The cut-off value for a positive test was 0.35 International Units(IU)/mL of interferon (IFN)-gamma in the sample after stimulation with the specific antigens, as suggested by the manufacturer. The task force decided to refer only those children positive to QFT-IT for isoniazid prophylaxis, since the exposed cohort had a priori a quite low probability of infection. Protocol dictated that children with a positive QFT-IT were referred for a chest X-ray and an additional clinical visit. An educational programme for the paediatricians of the exposed children, covering the clinical aspects of TB in that age group, was planned.

Tests whose results are reported here, were all performed from 18 August to 10 September, 2011. The table shows preliminary results of 1,340 tests for neonates whose parent or guardian consented to testing and examination. More potentially exposed neonates were tested after 10 September but the results are not yet known. Up to 10 September, a total of 118 (9%) positive QFT-ITs were obtained and only three (0.2%) indeterminate (low Mitogen Response, i.e. <0.5 IU/mL). The three children were retested after a month, after which they were responsive to the mitogen, and negative to QFT-IT. There was no clear trend from exposure (birth) month. Due to the immaturity of immune system, it was surprising to find that neonates scored QFT-IT positive under five weeks of age (11%, 9/79).

It is of note that, although not specified in the protocol, most QFT-IT positive infants subsequently were tested also with the TST, to check if the TST would confirm the positive QFT-IT. The infant diagnosed with active TB was both QFT-IT- and TST-positive, while the children

TABLE

Results of QuantiFERON TB gold by month of birth in the cohort of children potentially exposed to a nurse with active tuberculosis, Rome, Italy, January–July 2011 (n=1,340)

Month of birth in 2011	QuantiFERON TB gold	
	Total tested N ^a	Positive N (%)
January	122	15 (12)
February	170	20 (12)
March	209	21 (10) ^b
April	214	13 (6)
May	224	15 (7)
June	223	15 (7)
July	174	19 (11)
Unknown	4	0 (0)
Total	1,340	118 (9)

^a Three children's samples with low Mitogen Response (i.e. <0.5 IU/mL) were considered indeterminate; after a month these children were retested after which they were mitogen-responsive and QuantiFERON in-tube negative. For 15 cases, negative to gamma-interferon, Mitogen was not performed and for one case the result was missing.

^b Table does not include the only confirmed case of active tuberculosis that occurred in an infant born in March.

without active TB, who had a QFT-IT positive result, were TST negative. To date, no other person with active TB has been identified.

Unfortunately there are no estimates of QFT-IT sensitivity and specificity in newborns [16-20]. Therefore, to estimate the proportion of true and false positives, QFT-IT test results from a sample of unexposed children of the same age are needed, but ethical and practical issues make this problematic. On the other hand, the sensitivity of immune-based tests is known to be low, in particular in the first weeks after infection and birth. Furthermore, it is possible that some infected children test false negative to QFT-IT. For these cases an active surveillance of symptoms by parents and paediatricians has been planned.

In conclusion, in this investigation 118 of 1,340 (9%) newborns who had been exposed to a nurse with active TB were found to have a positive QFT-IT. The majority of the neonates with a positive QFT-IT were tested also by TST and found to be TST-negative. After two to nine months of follow-up, none of the QFT-IT-positive neonates progressed to active TB, indicating a low predictive value of this assay for progression to active TB in this population. The only case of active TB found in this cohort was positive, at the time of TB diagnosis, to both TST and QFT-IT. This cohort will be carefully followed for the next three years.

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