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Cost effectiveness of high resolution computed tomography with interferon-gamma release assay for tuberculosis contact investigation

Akiko Kowada*

Kojiya Haneda Healthcare Service, Ota City Public Health Office, Tokyo, Japan

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ABSTRACT

Background: Tuberculosis contact investigation is one of the important public health strategies to control tuberculosis worldwide. Recently, high resolution computed tomography (HRCT) has been reported as a more accurate radiological method with higher sensitivity and specificity than chest X-ray (CXR) to detect active tuberculosis. In this study, we assessed the cost effectiveness of HRCT compared to CXR in combination with QuantiFERON®-TB Gold In-Tube (QFT) or the tuberculin skin test (TST) for tuberculosis contact investigation.

Methods: We constructed Markov models using a societal perspective on the lifetime horizon. The target population was a hypothetical cohort of immunocompetent 20-year-old contacts with smear-positive tuberculosis patients in developed countries. Six strategies; QFT followed by CXR, QFT followed by HRCT, TST followed by CXR, TST followed by HRCT, CXR alone and HRCT alone were modeled. All costs and clinical benefits were discounted at a fixed annual rate of 3%.

Results: In the base-case analysis, QFT followed by HRCT strategy yielded the greatest benefit at the lowest cost ($US 6308.65; 27.56045 quality-adjusted life-years [QALYs])[year 2012 values]. Cost-effectiveness was sensitive to BCG vaccination rate.

Conclusions: The QFT followed by HRCT strategy yielded the greatest benefits at the lowest cost. HRCT chest imaging, instead of CXR, is recommended as a cost effective addition to the evaluation and management of tuberculosis contacts in public health policy.

1. Introduction

Tuberculosis (TB) is a widespread infectious and serious disease for global public health. To control TB, TB contact investigations play a very important role in public health policies not only by diagnosing latent tuberculosis infection (LTBI) and allowing chemoprophylaxis but also by earlier detection of active TB, often leading to treatment before appearance of symptoms of TB. The main approach for detecting active pulmonary TB is currently radiological examination by chest X-ray (CXR). However, low sensitivity and specificity of CXR are well known limitations. Recently, chest computed tomography has been reported as a more accurate and effective radiological method with higher sensitivity and specificity [1–4]. Multi-detector row computed tomography (MDCT) has greatly increased the clinical indications for CT and promotes to minimize excessive CT radiation exposure. High resolution CT (HRCT) images can be created from raw-data of MDCT without additional radiation [5–7].

Mycobacterium tuberculosis-specific interferon-gamma release assays (IGRAs) – QuantiFERON®TB Gold In-Tube (QFT) [Cellestis Limited, Chadstone, VIC, Australia] and T-SPOT®.TB (Oxford Immunotec, Oxford, UK) are now available and provide more accurate and sensitive diagnosis of *M. tuberculosis* infection with higher specificity than that of the tuberculin skin test (TST). They are not affected by bacillus Calmette-Guérin (BCG) vaccination and do not suffer from the booster phenomenon seen with repeated TSTs. However, these tests do not discriminate between active TB and LTBI and thus those testing positive are usually screened for active pulmonary TB using CXR. There are recent reports demonstrating the utility of using HRCT, rather than CXR, in combination with IGRAs for tuberculosis screening [7]. However, although more accurate, the purchase costs of HRCT and IGRAs are higher than CXR and TST and thus their overall cost effectiveness as mass TB screening tools warrants evaluation.

In this study, we assessed the cost effectiveness of HRCT versus CXR in combination with QFT or TST strategies for TB contact investigation to demonstrate the optimal screening method for contacts.

* Tel.: +81 3 3743 8315; fax: +81 3 3742 3116.
E-mail address: kowadaa@gmail.com

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2. Methods

2.1. Target population

Immunocompetent 20-year-olds contacts were chosen as a hypothetical cohort on lifetime horizon in developed countries.

2.2. Markov models

The following four clinical states were included in our model to represent the possible clinical states in the target population: (i) Well (no LTBI and no TB); (ii) LTBI; (iii) TB; (iv) Death. Decision-analytical calculations were performed using Tree Age Pro Healthcare Module 2009 (Tree Age Software Inc., Williamstown, MA, USA). Each cycle length was 1 year.

As this was a modeling study with all inputs and parameters derived from published literatures, ethics approval was not required.

Markov models were developed for six strategies: QFT followed by CXR, QFT followed by HRCT, TST followed by CXR, TST followed by HRCT, CXR alone and HRCT alone (Fig. 1). The contacts were stratified by BCG-vaccination status for TST strategies. Markov models are state transition models to calculate expected values, costs and utilities [8].

(1) QFT followed by CXR strategy: The contact undergoes QFT testing. If QFT is positive, active TB is detected on CXR, and the sputum smears and/or cultures are positive, the contact is treated per the standard 6-month protocol for active TB. If QFT is positive and active TB is not detected on CXR, the contact is treated per the standard 9-month isonicotinyl hydrazide (INH) chemoprophylaxis regimen for LTBI. If QFT is negative, the contact has no CXR and no need for follow-up. We considered the adherence and complication rates of chemoprevention [9,10]. We also estimated the recurrence of TB [11]. We used published estimates of sensitivity and specificity of QFT from a meta-analysis of developed country studies [12]. We used published estimates of sensitivity and specificity of CXR [13].

(2) QFT followed by HRCT strategy: The contact undergoes QFT testing. If QFT is positive, active TB is detected on HRCT, and the sputum smears and/or cultures are positive, the contact is treated per the standard 6-month protocol for active TB. If active TB is not detected on HRCT, the contact is treated per the standard 9-month INH chemoprophylaxis for LTBI. If QFT is negative, the contact has no HRCT and no need for follow-up. We used published estimates of sensitivity and specificity of HRCT [1–4].

(3) TST followed by CXR strategy: The contact undergoes TST testing. If TST induration diameter is $\geq$5 mm in non BCG-vaccinated contacts and $\geq$10 mm in BCG-vaccinated contacts, the contact undergoes CXR. If active TB is detected on CXR and the sputum smears and/or cultures are positive, the contact is treated per the standard 6-month protocol for active TB. If active TB is not detected on CXR, the contact is treated per the standard 9-month INH chemoprophylaxis protocol for LTBI. If TST induration diameter is <5 mm in non BCG-vaccinated contacts and <10 mm in BCG-vaccinated contacts, the contact has no CXR and no need for follow-up. We used published estimates of sensitivity and specificity of TST from a meta-analysis [14].

(4) TST followed by HRCT strategy: The contact undergoes TST testing. If TST induration diameter is $\geq$5 mm in non BCG-vaccinated contacts and $\geq$10 mm in BCG-vaccinated contacts, the contact undergoes HRCT. If TST is positive, active TB is detected on HRCT, and the sputum smears and/or cultures are positive, the contact is treated per the standard 6-month protocol for active TB. If active TB is not detected on HRCT, the contact is treated per the standard 9-month INH chemoprophylaxis protocol for LTBI. If TST induration diameter is <5 mm in non BCG-vaccinated contacts and <10 mm in BCG-vaccinated contacts, the contact has no HRCT and no need for follow-up.

(5) CXR strategy: The contact undergoes CXR. If active TB is detected on CXR and the sputum smears and/or cultures are positive, the contact is treated per the standard 6-month protocol for active TB. If active TB is not detected on CXR, the contact has no need for follow-up.

(6) HRCT strategy: The contact undergoes HRCT. If active TB is detected on HRCT and the sputum smears and/or cultures are positive, the contact is treated per the standard 6-month protocol for active TB. If active TB is not detected on HRCT, the contact has no need for follow-up.

2.3. Data sources, data, outcomes, and assumptions

Using MEDLINE, we undertook a search of the literature published from 1980 to October 27, 2012. We assume the adherence rate (the proportion of patients who accept LTBI treatment) of the standard 9-month INH chemoprophylaxis protocol, the probability of INH-induced hepatitis, and the efficacy (preventing progression from LTBI to TB) of the standard 9-month chemoprophylaxis [9,10]. We also assume the probability of successful active TB treatment [15]. Age-specific all-cause mortality rates were obtained from Japanese life tables [16]. Age-specific TB-related mortality rates were obtained from the database from Japanese tuberculosis surveillance [17] and the excess cancer mortality risk by MDCT radiation exposure was considered [18] (Table 1).

Data from meta-analyses were used for determining the sensitivities and specificities of QFT and TST (non BCG-vaccinated, BCG-vaccinated) [12,14]. The sensitivities and specificities of CXR and HRCT were obtained from studies conducted in numerous countries [1–4,13].

All costs were adjusted to 2012 Japanese yen, using the medical care component of the Japanese consumer price index [19], and were converted to US dollars, using the Organisation for Economic Co-operation and Development (OECD) purchasing power parity rate in 2009. Cost data were collected from various published sources [9,19,20]. The cost of QFT screening included the screening kits, one physician visit, and the labor cost for laboratory technicians. The cost of TST screening included the labor cost for the two physician visits and the TST reagents. The cost of CXR and HRCT included the material cost of CXR and HRCT, one physician visit, and the labor cost for radiological technicians. The costs of treating active TB, the standard 9-month INH chemoprevention, as well as the treatment of liver dysfunction was determined, based on published literature [9]. The costs of the smear and culture examinations of sputum were also considered when active TB was detected by CXR or HRCT.

The main outcome measure of effectiveness was quality-adjusted life-years (QALYs) gained. QALY is the life expectancy which takes into account both the quantity and quality of life.

Incremental cost, incremental effectiveness and incremental cost-effectiveness ratio (ICER) were calculated. Incremental cost is the increase or decrease in costs compared to the QFT followed by HRCT strategy. Incremental effectiveness is the increase or decrease in effectiveness compared to the QFT followed by HRCT strategy. ICER is the ratio of incremental cost per the incremental effectiveness. The lower ICERs correspond to better values. ICER of each screening arm was applied and compared. 'Dominated' means that the strategy costs more and is less effective than the QFT followed by HRCT strategy.

All costs and clinical benefits were discounted at a fixed annual rate of 3%. A discount rate of 3% was applied by convention.