Pulmonary tuberculosis (TB) remains a common worldwide infection that produces high mortality and morbidity, especially in developing countries. Latent TB infection (LTBI) is defined as a state of persistent infection, in the absence of clinical symptoms of active disease. When clinically manifest illness is present, the term TB, without further qualifications, is used to designate the disease. Given these definitions, both LTBI and TB may be considered different moments in a continual pathological process, and both conditions are usually distinguished on the basis of the presence (TB) or absence (LTBI) of clinical, laboratory, and chest radiography (CXR) findings.

Control of TB infection relies on the identification and preventive treatment of individuals who are latently infected with Mycobacterium tuberculosis (MtB). The diagnostic tests used to identify individuals with LTBI are the in vivo tuberculin skin test (TST) and the ex vivo interferon-γ release assays (IGRA); both are designed to identify an adaptive immune response against (but not necessarily a latent infection with) Mtb. The problem of LTBI screening has become more and more relevant in recent years because of the introduction of immunomodulatory biologic drugs in clinical practice, especially in the field of rheumatic diseases. In fact, tumor necrosis factor-α (TNF-α) antagonists can be the cause of either de novo TB infection or reactivation of LTBI. Therefore, different surveillance agencies for disease control and prevention have issued recommendations to ensure the detection and treatment of LTBI before TNF-α antagonist initiation.

This systematic review focuses on the role and value of CXR in TB diagnosis and screening for LTBI detection in patients who undergo medical treatment with biological drugs. The main objective of this work was to give evidence-based answers to relevant clinical issues regarding the value of diagnostic imaging in the screening for LTBI.

**Methods**

A systematic review of the medical literature was performed by searching PubMed up to January 2013, with no time limits, using the following MeSH terms as keywords in variable associations: “chest” or “thoracic” + “radiography” or “radiograph” or “x-rays” + “post primary tuberculosis” or “postprimary tuberculosis” or “post-primary tuberculosis” or “latent tuberculosis” or “tuberculosis reactivation.” “Chest” or “thoracic” + “radiography” or “radiograph” or “x-rays” + “tumor necrosis factor-alpha” or “tumor necrosis
factor-alpha antagonists” or “biologics” were used as additional keywords. A manual search of the references of the retrieved articles was performed. Articles in languages other than English or Italian were excluded. We included only original papers dealing with latent and post-primary TB imaging and diagnosis, with particular attention to those related to TB reactivation in patients under treatment with biologics.

Results
A total of 1111 papers were retrieved (Figure 1). A large number (936 articles) were initially excluded on the basis of the title or abstract, i.e., considered not pertinent. The remaining were analyzed according to the close relevance of their title or abstract. This method led us to read 157 articles, and at the end of the review process, 67 papers were selected. All included papers were in English. The remaining 90 articles were excluded because they were not pertinent or not focused on our topic.

What is the Current Role of CXR in the Screening for LTBI?
The World Health Organization once estimated that about one-third of the world’s population had been infected by Mtb, with 8.7 million new cases of infection in 20111. A complete diagnostic evaluation for TB infection should include medical history, physical examination, CXR, TST, serologic test (IGRA), microbiologic smears, and cultures. The gold standard for the diagnosis of TB is obtained by culturing Mtb from a specimen taken from the patient11,12,13, but owing to the slow-growth of this aerobic, non-motile, non-spore-forming rod11,14, diagnosis usually takes a long time. Worldwide clinical trials and post-marketing surveillance data have demonstrated an increased incidence of TB infection associated with anti-TNF-α agents10,15,16,17. The majority of these cases are presumed to result from a reactivation of an LTBI, while the rate of new infections is unknown. So, several studies have suggested screening patients for LTBI before anti-TNF-α therapy18,19, but it is currently not possible to identify the presence of living bacilli in subjects thought to have LTBI14,20,21,22,23,24,25. Different screening programs for LTBI detection in patients scheduled for medical treatment with biologics include as the first step the case history, TB risk factor assessment, and physical examination. CXR is used in conjunction with TST or IGRA, but its position in the screening procedure may vary among different guidelines and recommendations. The American College of Rheumatology panel and the National Psoriasis Foundation recommend screening to identify LTBI in patients with rheumatoid arthritis (RA) and psoriatic diseases who are scheduled for therapy with biologic agents, indicating TST.
and IGRA as the first screening tests. CXR is considered in the case of positive TST/IGRA. Other scientific societies suggest that CXR should be considered as the first step of the screening process. CXR is useful when TST results are unreliable, reading of the skin test is impractical, or the risk of transmission of undiagnosed cases is high, as occurs in institutional settings (jails, hospitals, longterm care facilities). It must be remembered that patients with RA could have an attenuated response to TST. In addition, the diagnosis of TB can be elusive, and symptomatic, culture-positive pulmonary TB with a normal CXR is not uncommon.

What is the Diagnostic Performance of CXR in the Detection of TB Infection?
CXR screening for TB/LTBI in high-risk populations may demonstrate findings consistent with prior and/or active infection. Apart from fibrous scarring of the lung parenchyma, there are specific CXR patterns indicative of prior and/or current TB infection. A Ghon lesion is a calcified tuberculous caseating granuloma that represents the sequela of primary TB infection. Ranke complex is the combination of a Ghon focus with enlarged or calcified hilar/mediastinal lymph nodes; Simon foci are apical lymphadenopathy (5%) that result from hematogenous hilar/mediastinal lymph nodes; Simon foci are apical consolidation in the lower lung fields and, when compared to the cases involving the upper lobes, it produces less cavitation and residual fibrotic changes, but more parenchymal atelectasis.

According to a joint statement issued by the American Thoracic Society and the US Centers for Disease Control and Prevention, subjects infected with Mtb, as evidenced by a positive TST, should be classified starting from clinical, radiographic, and bacteriologic findings into one of the following categories: (a) TB infection, no disease; (b) TB infection, clinically active; (c) TB infection, clinically inactive. CXR has a high negative predictive value for the presence of active TB. In the adult immunocompetent population, the frequency of false negative examinations is about 1%, increasing to 7%–15% in individuals seropositive for human immunodeficiency virus (HIV). The detection of any abnormality (parenchymal, lymph nodal, or pleural), with or without associated calcification, cannot give precise information on disease activity on a single screening CXR. Temporal evolution is the only variable that allows a radiographic differentiation between active and inactive disease.

CXR has been used for over a century to diagnose pulmonary TB; however, it is limited by modest specificity with a high interobserver variability in radiological reports. Different studies aimed to determine the sensitivity and specificity of CXR findings for the diagnosis of TB (Figure 2). Cohen, et al found a sensitivity of 73–79% and a specificity of 60–63% in a high-risk population. Similar results were found by den Boon, et al, who compared the diagnostic value of typical TB symptoms (cough, sputum production, fever, weight loss, night sweats, hemoptysis, anoxemia, and dyspnea) versus chest radiography in a TB prevalence survey. The presence of any abnormalities on CXR had the highest sensitivity for detecting subjects with bacteriologically positive TB (0.97, 95% CI 0.90–1.00), while the specificity for any detectable abnormalities was 0.67 (95% CI 0.64–0.70). For peculiar findings, such as miliary TB, it is possible to reach sensitivity values ranging from 59 to 69%, and specificity from 97 to 100%. The detection of enlarged lymph nodes in children has a sensitivity of 67% and a specificity of 59%. Performing an additional lateral view of the chest, the sensitivity increased by 1.8%, and specificity by 2.5%. A correct diagnosis of pulmonary TB on CXR is dependent on the reader’s expertise, because the technique of CXR interpretation is currently not well standardized. In this regard, several authors have attempted to introduce

Table 1. Most common tuberculosis (TB) findings on chest radiography.

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<th>TB Chest Radiography Findings</th>
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<td>Primary disease</td>
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<td>Lymphadenopathy (83–96%, decreases with age)</td>
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<td>Parenchymal opacities (on the same side as nodal enlargement; 78–84%)</td>
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<td>Obstructive atelectasis (by adjacent enlarged nodes, especially in children)</td>
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<td>Pleural effusion (29–38%)</td>
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<td>Post-primary disease</td>
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<td>Cavitations (40–45%)</td>
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<td>Parenchymal opacities situated in the apical and posterior segments of the upper lobes (83–85%) and the superior segment of the lower lobes (11–14%)</td>
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<td>Pleural effusion (18%)</td>
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<td>Tuberculomas (round or oval, sharply margined lesions, 0.5–4.0 cm)</td>
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<td>Hilar and mediastinal lymphadenopathy (5%)</td>
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<td>Endobronchial involvement (2–4%)</td>
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standardized scoring systems that would increase CXR sensitivity and specificity. Results of a recent metaanalysis indicate that none of the scoring systems that have been proposed from 1899 to 2012 was based on the exclusive use of imaging findings. In fact, only the multimodal integration of clinical, laboratory, and imaging data allows to improve the diagnostic performance of CXR, reaching an overall sensitivity and specificity of 96% and 46%, respectively. A simplified scoring system has been recently proposed, including 4 easy-to-recognize features on CXR: upper lobe opacities, cavities, unilateral pleural effusion, and mediastinal/hilar lymphadenopathy. The authors obtained a high negative predictive value (91.5%, 95% CI 87.1–94.7), but a low positive predictive value (49.4%, 95% CI 42.9–55.9). Eisenberg and Pollock assessed the frequency and spectrum of abnormalities on routine screening of CXR in the preemployment evaluation of healthcare workers with positive TST, finding that CXR is of low yield in the detection of active TB or increased LTBI reactivation risk, and provided no assistance in deciding which individuals to prioritize for LTBI treatment.

Computed tomography (CT) is a corroborative imaging modality to study TB. It is more sensitive than CXR in the detection of both localized and disseminated disease and mediastinal lymphadenopathy. Woodring, et al said that the first CXR diagnosis of TB is correct in only 49% of cases (i.e., 34% of primary TB and 59% of reactivation). Chest CT can effectively detect 80% of patients with active TB and 89% of those with inactive TB. CT is very useful when there is a disagreement between clinical and radiological findings and/or when imaging findings are equivocal or inconclusive. Subjects with normal or equivocal CXR may have findings indicative of active TB on chest CT. Eisenberg and Pollock assessed the frequency and spectrum of abnormalities on routine screening of CXR in the preemployment evaluation of healthcare workers with positive TST, finding that CXR is of low yield in the detection of active TB or increased LTBI reactivation risk, and provided no assistance in deciding which individuals to prioritize for LTBI treatment.

Findings suggestive of active TB were detected by CT in 17 (32.7%) of the 52 subjects with a high probability of infection (30 subjects who were IGRA-positive and 22 subjects in whom the TST induration size was ≥ 20 mm). Collectively, among 21 (1.1%) patients with TB, all were TST-positive, 12 (57.1%) were IGRA-positive, and active TB was diagnosed by CT, but not by CXR, in 11 subjects.

When compared to the conventional approach with TST and CXR, the combined use of IGRA and chest CT in TST-positives may be more effective in differentiating between active TB, LTBI, and non-infected subjects in a contact investigation. On the other hand, as commented by Marais, et al, the use of chest CT for screening of asymptomatic contacts is not safe because it leads to overdiagnosis of “active TB,” exposing patients to high radiation doses and undermining confidence in existing screening tools. Introduction of CT is considered only in certain groups of individuals at high risk for TB reactivation, such as immunocompromised patients. A more effective detection of active TB would prevent the prescription of
inappropriate LTBI treatment and the subsequent development of drug resistance. Lee, et al evaluated the advantages of chest CT in a TB outbreak investigation in the South Korean army. Lesions indicative of active TB were detected in 18 participants (21%), including 9 without any lesion on CXR and positive results in either TST or IGRA. The authors conclude that CT can be helpful for differentiating active TB from LTBI. Otherwise this diagnostic tool should be carefully considered, taking into account its risk and cost. Other authors commented on the article by Lee, et al, suggesting that chest CT leads to a significantly higher radiation dose than CXR, and to higher costs. They underlined that the use of CT as a screening test during TB outbreak investigations is not justified, but it could only be performed in symptomatic patients, and in certain high-risk groups. The importance of identifying LTBI has become even greater since TNF-α antagonists have been introduced in routine clinical practice for the treatment of RA and other inflammatory rheumatologic disorders. Tannus Silva, et al evaluated the advantages of CT as a screening tool for LTBI detection in patients with RA. CT showed changes compatible with LTBI in 52.9% of patients.

Figure 3. Miliary tuberculosis from hematogenous seeding. Posteroanterior (A) and lateral (B) chest radiographs. Panel A demonstrates peribronchovascular interstitial thickening with a micronodular appearance. Computerized tomography (CT) image on the axial plane (C) shows multiple micronodules disseminated in both lungs, and the reconstructed CT image with maximum intensity projection technique clearly demonstrates their centrilobular location (D).
including 8 of the 11 patients with negative TST and IGRA. These results underline the importance of a combined use of different diagnostic modalities for an effective detection of LTBI.

What About “Atypical” Patterns and Peculiar Conditions?
Since the 1950s the incidence of TB infection in industrialized countries has decreased markedly. However, in recent years this trend has started to reverse because of changing population characteristics, such as an influx of immigrants from high-incidence areas and the wide diffusion of the HIV. In comparison to the past, it mainly affects younger adults who belong to certain groups, such as immunocompromised patients. These patients may present with “atypical” or “unusual” patterns on CXR (i.e., solitary pleural effusion, miliary pattern, lesions in the lung bases, solitary mediastinal or hilar lymphadenopathies). HIV-associated pulmonary TB has CXR patterns that are dependent on the level of immunosuppression.

Correlating CXR and CD4 T lymphocyte levels, a significantly higher prevalence of mediastinal and/or hilar lymphadenopathy and a lower prevalence of cavitation were identified in patients with a CD4 T lymphocyte count of less than 200/mm³. With the worsening of immunosuppression, a higher incidence has been reported of miliary pattern, extrapulmonary disease, and atypical presentation. CT evaluation of pulmonary TB in HIV-seropositive patients with normal CXR usually demonstrates subtle abnormalities, and some authors have identified some specific CT patterns such as multiple parenchymal nodules, tuberculosis, and lymphadenopathy. Lymphadenopathy can present on CT images with a central low attenuation area and peripheral enhancement, as for example in immunocompetent patients. HIV-seropositive patients had a lower prevalence of localized parenchymal disease and a higher prevalence of disseminated disease at CT.

When a child has positive TST, normal CXR, and no symptoms, the child is considered to have LTBI. When the findings are positive TST, pathological CXR, and symptoms, the child is considered to have TB. In a child in whom previous contact with TB is certain, the presence of positive TST and pathological CXR with or without symptoms suggests a diagnosis of TB. On the basis of indirect signs of low specificity, symptoms, CXR, and TST, the diagnosis of primary TB is difficult to achieve. CT is recommended if CXR is equivocal. An abnormal thoracic CT occurs in 92.8% of children with positive TST and negative CXR. So, Garrido, et al suggested that, in children younger than 4 years with positive TST and normal CXR, it would be advisable to perform CT. A recent study on post-liver transplantation patients demonstrated that a pretransplant chest CT scan is more useful to show LTBI than a CXR in a TB endemic country. An increased risk for pulmonary TB is associated with findings such as a “tree-in-bud” appearance (indicative of endobronchial spread), lobular consolidation, and large nodules on CT scans.

In subgroups of individuals with a high probability of infection, the combined use of TST, IGRA, CXR, and CT is effective in differentiating between active TB, LTBI, and uninfected subjects. The usefulness of chest CT among immunocompromised patients should be further investigated.

Statement
CXR must be performed after positive TST/IGRA. Because patients undergoing medical treatment with biologics are a group at high risk for TB reactivation, CT may be indicated when faced with a positive TST/IGRA and inconclusive CXR findings.

The role of CXR in the detection of LTBI can be summarized as follows:

- Chest radiography for the diagnosis of pulmonary TB has good sensitivity but poor specificity
- Radiographic diagnosis of active disease can only be reliably made on the basis of temporal evolution of pulmonary lesions
- The radiographic diagnosis of TB can be elusive, and symptomatic, culture-positive pulmonary TB with a normal CXR is not uncommon
- In specific subgroups of patients, including candidates for anti-TNF-α treatment, the combined approach based on immunological tests, CXR, and CT could be very useful for LTBI detection

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