Inhaled corticosteroids and the increased risk of pulmonary tuberculosis: a population-based case–control study

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SUMMARY

Aims: The association between inhaled corticosteroid (ICS) use and pulmonary tuberculosis (TB) development is uncertain. We conducted a population-based case–control study to investigate whether ICS use increases the risk of developing TB. Methods: Tuberculosis patients aged 18 years and older were identified using the National Health Insurance Research Database (NHIRD) in Taiwan between 2002 and 2010. Each TB patient was frequency matched to four control patients according to age, sex and index year. We retrospectively followed up the medications and comorbid medical conditions for the 5 years prior to the index date. We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) of TB development using multiple logistic regression models. Results: Most of the study participants were men (68.7%), and the mean age among the 8091 TB patients and 32,364 comparison participants was 61.3 ± 18.6 years. After adjusting for potential covariates, ICS use caused a 2.04-fold increased risk of developing TB (adjusted OR: 2.04, 95% CI: 1.78–2.33). When considering dose-response and adjusting for potential covariates, ICS and oral corticosteroids (OCS) use remained independent risk factors and exhibited a dose-response relationship of TB development. The multiplicative increased risk of TB was also significant in patients using ICS and OCS compared with patients not using ICS and OCS (adjusted OR: 4.31, 95% CI: 3.39–5.49). Previous TB history exhibited the greatest risk of TB development among the comorbidities (adjusted OR: 8.50, 95% CI: 7.52–9.61). Conclusion: Long-term ICS use may increase the risk of TB.

What’s known

• Long-term oral steroids (OCS) and disease-modifying anti-rheumatic drugs increase the risk of pulmonary tuberculosis (TB).

What’s new

• Long-term inhaled corticosteroids (ICS) use caused a 2.04-fold increased risk of developing TB.
• ICS exhibited a dose-response relationship of TB development.
• The multiplicative increased risk of TB was also significant in patients using ICS and OCS compared with patients without using ICS and OCS.

Introduction

Inhaled corticosteroids (ICS) are medicines delivered directly into the lungs to reduce the inflammatory process caused by asthma or chronic obstructive pulmonary diseases (COPD) (1–3). In general, ICS are preferred to oral corticosteroids (OCS) because their anti-inflammatory effect is directed at the airways, which reduces the risk of unwanted systemic effects.

*Mycobacterium tuberculosis* (MTB) enters humans through the inhalation of droplet nuclei. After deposition in the alveoli, MTB is engulfed by alveolar macrophages, but survives and multiplies within the macrophages. Proliferating MTB kills macrophages and is released, which produces a response from the immune system. Successful containment of MTB depends on the immune system. Therefore, exposure may cause clearance of MTB, persistent latent infection, and progression to pulmonary tuberculosis (TB) disease. A healthy immune system typically eliminates MTB, but numerous diseases and medications can weaken the immune system to TB development.

The incidence of TB was 55 patients per 100,000 population in Taiwan in 2012, which is higher than that in Canada (4.6 patients per 100,000 population) and in the USA (3.2 patients per 100,000 population) (4–6). Previous studies have reported that the conditions that increase the risk of subsequent TB development include diabetes mellitus (DM) (7), cancer (8), liver cirrhosis (9,10), end-stage renal disease (11), previous TB (12), tobacco use (13), human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (14) and pneumoconiosis (15). Several medications modifying the immune system, such as glucocorticoids and disease-modifying antirheumatic drugs (DMARDs), including tumour necrosis factor-alpha (TNF-α) blockers and methotrexate, have been reported to increase the risk of TB.
Inhaled corticosteroids and pulmonary tuberculosis

Whether ICS use increases the risk of developing TB remains controversial (20,21). We conducted a population-based case–control study to investigate the relationship between ICS use and the risk of TB development.

Methods

Data source
The data analysed in this study were retrieved from the National Health Insurance Research Database (NHIRD), a database established and maintained by the National Health Research Institutes (NHRI). Before releasing medical claims data to the NHRI, the Bureau of National Health Insurance scrambles the identification codes of each patient. The National Health Insurance (NHI) programme in Taiwan has been operating since 1995. The programme covers approximately 99% of Taiwan’s 23.74 million people and was contracted by 97% of hospitals and clinics by the end of 2009 (22). We used a systemic sampling of the patient data of 1 million people from all insured beneficiaries that was released by the NHRI as the Longitudinal Health Insurance Database (LHID). The NHRI reported no significant variations in age and sex between the LHID and all insurants. The high accuracy and validity of diagnoses in the NHIRD have been described in previous studies (23,24). International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes were used for diagnoses. This study was approved by the Institutional Review Board of Taichung Hospital (IRB-I102013).

Study patients
We conducted a population-based case–control study to investigate the association between ICS use and TB development. The TB patients who were 18 years and older received medical care at least three times, including outpatient visits and hospitalizations, for a principal diagnosis of TB (ICD-9-CM codes 011-018) during 2002–2010. The date of TB diagnosis served as the index date. For each TB patient identified, four insured people without TB were randomly selected, frequency matched for the same year, and designated as the non-TB controls. Patients and controls were matched for age and sex. We retrospectively observed the medications and comorbidities of each participant for the 5 years prior to the index date.

Exposure variables

Inhaled corticosteroid
All forms of prescribed ICS were evaluated during the 5-year period preceding the index date. Four ICS are currently available in Taiwan: beclomethasone dipropionate (beclomethasone), budesonide, fluticasone propionate (fluticasone) and ciclesonide, and are dispensed alone or in a combination inhaler with an inhaled β-agonist. We estimated the total quantity of ICS during follow-up according to the duration of treatment to obtain the average daily doses, which were then converted to the equivalent dose of fluticasone in micrograms per day (1). Furthermore, we stratified the patients into four groups based on daily equivalent fluticasone doses: no fluticasone use, low dose (100–250 μg/day), medium dose (250–500 μg/day) and high dose (> 500 μg/day) (1).

Covariates
In addition to age and sex, comorbidities were also analysed. The pre-existing comorbidities and conditions included DM (ICD-9-CM 250), cancer (ICD-9-CM 140–208), liver cirrhosis (ICD-9-CM 571.2, 571.5), end-stage renal failure (ICD-9-CM 585), HIV/AIDS (ICD-9-CM 042), previous TB (ICD-9-CM 137.0), tobacco use (ICD-9-CM 305.1) and pneumoconiosis (ICD-9-CM 500, 502, 503, 505). Moreover, we divided the total amount of intravenous and OCS received during follow-up to determine average daily doses, which were then converted to the equivalent doses of oral prednisolone in milligrams per day (16). We also stratified the average daily doses of OCS into four groups: no OCS use, low dose (1–10 mg/day), medium dose (10–15 mg/day) and high dose (> 15 mg/day). In addition to OCS, DMARDs were also recorded and analysed.

Statistical analysis
We compared the differences in demographical characteristics (including age and sex), comorbidities and the medications received between the TB cohort and the comparison cohort by using a χ² analysis for the categorical variables and t-tests for the continuous variables. We conducted univariate and multivariate logistic regression analyses on the potential predictors and obtained p < 0.10 from bivariate analyses. The odds ratios (ORs) and 95% confidence intervals (CIs) of dichotomous and categorical risk variables on the binary outcome variables were calculated. All analyses were conducted using SPSS 17.0 software (SPSS Inc., Chicago, IL), and all of the tests were performed at the two-tailed significance level of 0.05.

Results

Comparison of the demographical characteristics and medical conditions between TB patients and matched controls
A total of 8091 TB patients and 32,364 non-TB patients were analysed. Men comprised 68.7% of the
The mean age of both cohorts was 61.3 ± 18.6 years. Nearly half of the patients in both cohorts were aged 65 years and older. The TB patients exhibited a higher prevalence of comorbidities than the non-TB patients did. Because of the number of HIV/AIDS patients was low in both cohorts, the comorbidity of HIV/AIDS did not receive additional analyses. Furthermore, the TB patient cohort exhibited a higher proportion of ICS, OCS and DMARD use than the non-TB cohort did (Table 1).

Factors influencing the risk of TB development

Table 2 shows the crude and adjusted ORs for potential factors influencing the risk of TB development. After adjusting for potential covariates, ICS users exhibited a 2.04-fold greater risk of subsequent TB development compared with non-ICS users (95% CI: 1.78–2.33). Among the comorbidities, patients that presented a previous TB history exhibited the greatest risk for developing TB (adjusted OR: 8.50, 95% CI: 7.52–9.61). Patients using OCS and DMARDs also exhibited an increased risk of subsequent TB development (adjusted OR: 3.03, 95% CI: 2.70–3.41 and adjusted OR: 2.57, 95% CI: 1.72–3.84, respectively).

The dose-response relationship and interaction between ICS and OCS on the risk of TB development

The risk of TB development in patients using ICS progressively increased as the daily dose of ICS increased compared with patients not using ICS, after adjusting for potential covariates (low dose with adjusted OR: 1.42, 95% CI: 1.03–1.96; medium dose with adjusted OR: 1.92, 95% CI: 1.52–2.42; and high dose with adjusted OR: 2.32, 95% CI: 1.95–2.75). Patients using OCS also exhibited a dose-response relationship of developing TB compared with patients not using OCS, after adjusting for covariates (low dose with adjusted OR: 2.70, 95% CI: 2.39–3.05; medium dose with adjusted OR: 4.15, 95% CI: 2.35–7.32; and high dose with adjusted OR: 8.68, 95% CI: 5.35–14.08). When considering the interaction between ICS and OCS, the multiplicative increased risk of TB was significant in patients using

| Table 1 Comparison of demographical characteristics and medical conditions between tuberculosis patients and matched controls |
|---|
| **Tuberculosis** | No (N = 32,364), n (%) | Yes (N = 8091), n (%) | p-value |
| **Sex** | | | |
| Men | 22,220 (68.7) | 5555 (68.7) | Matched |
| Women | 10,144 (31.3) | 2536 (31.3) | |
| **Age (mean and SD, years)** | | | |
| 18–40 | 5316 (16.4) | 1329 (16.4) | Matched |
| 40–64 | 11,068 (34.2) | 2767 (34.2) | |
| ≥ 65 | 15,980 (49.4) | 3995 (49.4) | |
| **Respiratory diseases** | | | |
| Asthma (ICD 4930-4939) | 1532 (4.7) | 1017 (12.6) | < 0.001 |
| COPD (ICD 491, 492, 496) | 3390 (10.5) | 2342 (28.9) | < 0.001 |
| **Comorbidities** | | | |
| DM (ICD 250) | 3944 (12.2) | 1605 (19.8) | < 0.001 |
| Cancer (ICD 140-208), catastrophic illness | 1404 (4.3) | 400 (4.9) | 0.01 |
| Liver cirrhosis (ICD 571.2, 571.5), catastrophic illness | 53 (0.2) | 24 (0.3) | 0.01 |
| End-stage renal disease (ICD 585), catastrophic illness | 210 (0.6) | 126 (1.6) | < 0.001 |
| AIDS (ICD 042), catastrophic illness | 3 (0.01) | 19 (0.2) | < 0.001 |
| Previous TB (ICD 137.0) | 411 (1.3) | 879 (10.9) | < 0.001 |
| Tobacco use (ICD 305.1) | 212 (0.7) | 95 (1.2) | 0.002 |
| Pneumoconiosis (ICD-9-CM 500, 502, 503, 505) | 211 (0.7) | 145 (1.8) | < 0.001 |
| **Medications** | | | |
| ICS | 643 (2.0) | 510 (6.3) | < 0.001 |
| OCS | 733 (2.3) | 679 (8.4) | < 0.001 |
| DMARD | 57 (0.2) | 52 (0.6) | < 0.001 |

ICS, inhaled corticosteroids; OCS, oral glucocorticoids; DMARD, diseases modifying antirheumatic drugs.
ICS and OCS compared with those not using ICS and OCS (adjusted OR: 4.31, 95% CI: 3.39–5.49) (Table 3). Figure 1 depicts the risk of TB development using ICS according to daily exposed dose and exhibits significant dose-response.

**Discussion**

This study indicates the effect of ICS quantity on the risk of subsequent TB development after adjusting for potential covariates. The patients using ICS exhibited a 2.04-fold increased risk for developing TB after adjusting for covariates (adjusted OR: 2.04, 95% CI: 1.78–2.33). Moreover, the dose-response effect of ICS on the risk of TB development was also significant. Shu et al. conducted a study on patients with COPD at a single hospital and observed that using a high dose of ICS was an independent risk factor for developing TB (25). Shu et al. did not evaluate whether the study participants received ICS or OCS from healthcare institutions other than the study hospital. Brassard et al. (21) indicated that exposure to ICS is associated with an increased TB risk in OCS nonusers, but it was not associated with an increased risk of TB in OCS users in Quebec, Canada. However, the TB incidence rate is low in Canada. The discrepancies in the described findings might reflect true variations in disease occurrence among various populations and environmental exposure.

Several mechanisms are used to explain that glucocorticoids may increase the risk of TB. Systemic glucocorticoids exert profound effects on cellular immune response, which inhibits TB development. The joint statement of the American Thoracic Society and the Centres for Disease Control and Prevention in the USA acknowledged that 15 mg/day or more of oral prednisolone administered for 1 month or longer is a risk factor of TB development (26). Jick et al. indicated that receiving 7.5 mg/day of oral prednisolone or an equivalent may increase the risk of TB development (16). In our study, long-term use of OCS, even at a low dose of 1–10 mg/day, exhibited an increased risk of TB development and displayed a dose-response effect.

Although the TB cohort in this study exhibited a higher prevalence of pre-existing comorbidities and immunosuppressive medicines associated with the development of TB than did the comparison cohort, ICS remained an independent risk factor for developing TB after adjusting for covariates. A high dose of an ICS, 1000 μg of inhaled fluticasone, was estimated to be equivalent to approximately 10 mg of oral prednisolone daily when the systemic effect was evaluated by suppressing serum cortisol (27). Recently, Lee et al. demonstrated that ICS use increased the risk of TB. ICS could reduce the local immunity of the lung (28). Our study examined the effects of 5-year ICS exposure on TB development, which might

| Table 2 | Crude and adjusted odds ratios for the factors influencing the risk of TB development |
|----------|---------------------------------|
|          | Crude | Adjusted |
|          | OR    | 95% CI  | OR    | 95% CI  |
| ICS      |       |        |       |        |
| No       | 1 (reference) | 1 (reference) |
| Yes      | 3.32  | 2.95, 3.74*** | 2.04  | 1.78, 2.33*** |
| Comorbidities |       |        |       |        |
| DM       | 1.78  | 1.67, 1.90*** | 1.70  | 1.59, 1.81*** |
| Cancer   | 1.15  | 1.02, 1.29*   | 0.99  | 0.87, 1.11 |
| Liver cirrhosis | 1.81  | 1.12, 2.94*   | 1.64  | 0.99, 2.73 |
| End-stage renal disease | 2.42  | 1.94, 3.03*** | 2.01  | 1.59, 2.54*** |
| Previous TB | 9.48  | 8.41, 10.68*** | 8.50  | 7.52, 9.61*** |
| Tobacco use | 1.80  | 1.41, 2.98**  | 1.69  | 1.31, 2.18*** |
| Pneumocociosis | 2.78  | 2.25, 3.44*** | 1.80  | 1.42, 2.27*** |
| OCS      |       |        |       |        |
| No       | 1 (reference) | 1 (reference) |
| Yes      | 3.95  | 3.55, 4.40*** | 3.03  | 2.70, 3.41*** |
| DMARD    |       |        |       |        |
| No       | 1 (reference) | 1 (reference) |
| Yes      | 3.67  | 2.52, 5.3423*** | 2.57  | 1.72, 3.84*** |

ICS, inhaled corticosteroids; OCS, oral glucocorticoids; DMARD, diseases modifying antirheumatic drugs. *p < 0.05, **p < 0.01, ***p < 0.001.
explain the long-term immunity effect of ICS. This effect may become severe in TB-endemic areas because suppressing the defence mechanism against MTB in the airway may increase the risk of TB development (25). Despite ICS become pivotal drugs in asthma and COPD management, it is necessary to appropriately select the patients in need to receive ICS among COPD and asthmatics (29).

Most of the TB patients in this study were men, and nearly half of the patients were older people; this is consistent with the findings of previous studies (4,30). Patients with a previous TB history exhibited an 8.5-fold greater risk factor for TB development compared with those who without a previous TB history. This finding is consistent with that of a previous study (25). TB recurrences may be caused by both endogenous reactivation and exogenous reinfection by a new strain (31,32). Reactivation TB is caused by a remotely acquired TB infection that is generally associated with the progression of the disease from an infection acquired in the past and often in another location (33,34).

Table 3 Odds ratios and 95% confidence interval of inhaled corticosteroids and oral glucocorticoids on the risk of TB development

| ICS (fluticasone equivalent) | TB patients (n/N) | % | Odds ratio (95% CI) of TB development |
|-----------------------------|------------------|---|-------------------------------------|
| None                        | 7581/39,302      | 19.3 | 1 (reference)                       |
| Low dose (100–250 µg/day)   | 100/262          | 38.2 | 2.58 (2.01, 3.32)***                |
| Medium dose (250–500 µg/day)| 113/266          | 42.5 | 3.09 (2.42, 3.95)***                |
| High dose (> 500 µg/day)    | 297/625          | 47.5 | 3.79 (3.23, 4.44)***                |
| p for trend                 |                  |     |                                     |

| OCS (Prednisolone equivalent) | TB patients (n/N) | % | Odds ratio (95% CI) of TB development |
|-------------------------------|------------------|---|-------------------------------------|
| No                            | 7412/39,043      | 19.0 | 1 (reference)                       |
| 1–10 mg/day                   | 595/1279         | 46.5 | 3.71 (3.32, 4.16)***                |
| 10.1–14.9 mg/day              | 27/51            | 52.9 | 4.80(2.77, 8.33)***                |
| ≥ 15 mg/day                   | 57/82            | 69.5 | 9.73(6.08, 15.58)***               |
| p for trend                   |                  |     |                                     |

| ICS and OCS                   | Odds ratio (95% CI) of TB development |
|-------------------------------|-------------------------------------|
| ICS(−), OCS(−)                | 1 (reference)                       |
| ICS(+), OCS(−)                | 3.02 (2.63, 3.48)***               |
| ICS(−), OCS (+)               | 3.82 (3.38, 4.30)***               |
| ICS (+), OCS (+)              | 5.25(4.17, 6.60)***                |
| p for interaction             |                                     |

ICS, inhaled corticosteroids; OCS, oral glucocorticoids. *Adjusted OR: multivariable analysis including comorbidities and medications.
*p < 0.05, **p < 0.01, ***p < 0.001.
were used for assessing the increased risk of TB development.

However, several limitations must be considered when interpreting these findings. First, the NHIRD does not provide detailed information, such as a history of recent contact with a person infected with TB and the presence of abnormal TB-associated findings on a chest X-ray, which are potential confounding factors for this study. However, these factors may be randomly distributed in the two large cohorts exposed to an endemic area. Second, the daily doses of ICS and OCS were calculated by dividing the total quantity of the prescribed drugs by the follow-up duration. The estimation can be used only to evaluate the exposure doses rather than the patients’ adherence.

In conclusion, this nationwide study of 8091 TB patients and 32,364 non-TB patients indicated that long-term use of ICS is associated with a 2.04-fold increased risk of developing TB. The long-term use of OCS was also associated with a 3.03-fold increased risk of TB development. These risks increased as the daily dose increased. The patients who presented a previous history of TB exhibited an 8.50-fold greater risk of TB development than those who did not. The findings indicate that clinicians must consider TB screening when prescribing the long-term use of ICS and OCS to patients.

**Author contributions**

Wei-Sheng Chung, John Y. Chiang: conception and design. Wei-Sheng Chung, Yung-Fu Chen: administrative support. Wei-Sheng Chung, John Y. Chiang, Yung-Fu Chen: data analysis and interpretation. All authors contributed to collection and data assembly, manuscript preparation and approved the final version of the manuscript.

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**References**

1 Bateman ED, Hurd SS, Barnes PJ et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31: 143–78.
2 Man SF, Sin DD. Inhaled corticosteroids in chronic obstructive pulmonary disease: is there a clinical benefit? *Drugs* 2005; 65: 579–91.
3 Gartlehner G, Hansen RA, Carson SS, Lohr KN. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. *Ann Fam Med* 2006; 4: 253–62.
4 CDC. Taiwan Tuberculosis Control Report, 2012. In: Chung FY, Shi WY, Chou JH, Chen YW, Chuang JH, Chen CH, Yang SL, Lo HY, eds. *Centers for Disease Control. R.O.C.* (Taiwan): Department of Health, 2012.
5 CDC. Reported Tuberculosis in the United States, 2012. In: U.S. *Department of Health and Human Services. Atlanta, GA: CDC, 2013.*
6 Canada PHAs. Tuberculosis in Canada 2010. In: *Centre for Communicable Diseases and Infection Control. Ottawa: Public Health Agency of Canada, 2012.*
7 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008; 5: e152.
8 Kamboj M, Sempowitz KA. The risk of tuberculosis in patients with cancer. *Clin Infect Dis* 2006; 42: 1592–5.
9 Thulstrup AM, Molle I, Svendsen N, Sorensen HT. Incidence and prognosis of tuberculosis in patients with cirrhosis of the liver. A Danish nationwide population based study. *Epidemiol Infect* 2000; 124: 221–5.
10 Baijal R, Pravenekumar HB, Amarpurkar DN, Nagaraj K, Jain M. Prevalence of tuberculosis in

patients with cirrhosis of liver in western India. *Trav Dent* 2010; 40: 163–4.
11 Hu HY, Wu CY, Huang N, Chou YJ, Chang YC, Chu D. Increased risk of tuberculosis in patients with end-stage renal disease: a population-based cohort study in Taiwan, a country of high incidence of end-stage renal disease. *Epidemiol Infect* 2014; 142: 191–9.
12 Lin CY, Chen TC, Lu PL et al. Effects of gender and age on development of concurrent extrapulmonary tuberculosis in patients with pulmonary tuberculosis: a population based study. *PLoS ONE* 2013; 8: e63936.
13 Slama K, Chiang CY, Enarson DA et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2007; 11: 1049–61.
14 Corbett EL, Watt CJ, Walker N et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009–21.
15 Chow KC, Leung CC, Tam CM. Tuberculosis risk factors in a silicotic cohort in Hong Kong. *Int J Tuberc Lung Dis* 2001; 5: 177–84.
16 Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum* 2006; 55: 19–26.
17 Bellofiore B, Matarese A, Balato N et al. Prevention of tuberculosis in patients taking tumor necrosis factor-alpha blockers. *J Rheumatol Suppl* 2009; 83: 76–7.
18 Kim HA, Yoo CD, Baek HJ et al. *Mycobacterium tuberculosis* infection in a corticosteroid-treated rheumatoid disease patient population. *Clin Exp Rheumatol* 1998; 16: 9–13.
19 Brassard P, Kezouh A, Suisse S. Antirheumatic drugs and the risk of tuberculosis. *Clin Infect Dis* 2006; 43: 717–22.
20 Bahceciler NN, Nuhoglu Y, Nursoy MA, Kodalli N, Barlan IB, Basaran MM. Inhaled corticosteroid therapy is safe in tuberculosis-positive asthmatic children. *Pediatr Infect Dis J* 2008; 19: 215–8.
21 Brassard P, Suisse S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *Am J Respir Crit Care Med* 2011; 183: 675–8.
22 Cheng TM. Taiwan’s National Health Insurance system: high value for the dollar. In: Okma KGH, Crippelli L, eds. *Six Countries, Six Reform Models: The Health Reform Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan. Hackensack, NJ: World Scientific, 2009; 71–204.
23 Chung WS, Peng CL, Lin CL et al. Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. *Ann Rheum Dis* 2013; (in press). doi:10.1136/annrheumdis-2013-203380.
24 Chung WS, Lin CL, Ho FM et al. Asthma increases pulmonary thromboembolism risk: a nationwide population cohort study. *Eur Respir J* 2014; 43: 801–7.
25 Shu CC, Wu HD, Yu MC et al. Use of high-dose inhaled corticosteroids is associated with pulmonary tuberculosis in patients with chronic obstructive pulmonary disease. *Medicine (Baltimore)* 2010; 89: 53–61.
26 Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA) and the sections of this statement. *Am J Respir Crit Care Med* 1999; 2000(161): S221–47.
27 Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999; 159: 941–55.

28 Lee CH, Kim K, Hyun MK, Jang EJ, Lee NR, Yim JJ. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax* 2013; 68: 1105–13.

29 Louis R, Schleich F, Barnes PJ. Corticosteroids: still at the frontline in asthma treatment? *Clin Chest Med* 2012; 68: 1105–13.

30 Chung WS, Chang RE, Guo HR. Variations of care quality for infectious pulmonary tuberculosis in Taiwan: a population based cohort study. *BMC Public Health* 2007; 7: 107.

31 Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. *Int J Tuberc Lung Dis* 2007; 11: 828–37.

32 Chiang CY, Riley LW. Exogenous reinfection in tuberculosis. *Lancet Infect Dis* 2005; 5: 629–36.

33 Barnes PF, Cave MD. Molecular epidemiology of tuberculosis. *N Engl J Med* 2003; 349: 1149–56.

34 Ricks PM, Cain KP, Oeltmann JE, Kammerer JS, Moonan PK. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005-2009. *PLoS ONE* 2011; 6: e27405.

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