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Tuberculosis and the risk of infection with other intracellular bacteria: a population-based study

M. A. HUAMAN[1,2]*, C. T. FISKE[1,2], T. F. JONES[2,3], J. WARKENTIN[2,3], B. E. SHEPHERD[2,4], L. A. INGRAM[3], F. MARURI[1,2,3] AND T. R. STERLING[1,2]

[1] *Division of Infectious Diseases, Department of Medicine, Vanderbilt University, Nashville, TN, USA*
[2] *Vanderbilt Tuberculosis Center, Vanderbilt University, Nashville, TN, USA*
[3] *Tennessee Department of Health, Nashville, TN, USA*
[4] *Department of Biostatistics, Vanderbilt University, Nashville, Tennessee, USA*

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SUMMARY

Persons who develop tuberculosis (TB) may have subtle immune defects that could predispose to other intracellular bacterial infections (ICBIs). We obtained data on TB and five ICBIs (*Chlamydia trachomatis, Salmonella* spp., *Shigella* spp., *Yersinia* spp., *Listeria monocytogenes*) reported to the Tennessee Department of Health, USA, 2000–2011. Incidence rate ratios (IRRs) comparing ICBIs in persons who developed TB and ICBIs in the Tennessee population, adjusted for age, sex, race and ethnicity were estimated. IRRs were not significantly elevated for all ICBIs combined [IRR 0·87, 95% confidence interval (CI) 0·71–1·06]. *C. trachomatis* rate was lowest in the year post-TB diagnosis (IRR 0·17, 95% CI 0·04–0·70). More *Salmonella* infections occurred in extrapulmonary TB compared to pulmonary TB patients (IRR 14·3, 95% CI 1·67–122); however, this appeared to be related to HIV co-infection. TB was not associated with an increased risk of other ICBIs. In fact, fewer *C. trachomatis* infections occurred after recent TB diagnosis. Reasons for this association, including reduced exposure, protection conferred by anti-TB drugs or macrophage activation by *Mycobacterium tuberculosis* infection warrant further investigation.

Key words: Chlamydia, epidemiology, *Salmonella*, tuberculosis (TB).

INTRODUCTION

The host immune response against *Mycobacterium tuberculosis* infection is orchestrated by the innate and cellular arms of the immune system. Macrophages and dendritic cells initially recognize *M. tuberculosis* via pathogen-recognition receptors such as Toll-like receptors (TLRs) and NOD2. This results in the production of cellular mediators such as interleukin (IL)-1, IL-6 and IL-12 that in turn activate CD4+ and CD8+ T lymphocytes. Activated T cells produce interferon (IFN)-γ and other mediators that are involved in mycobacterial killing, partly through activation of macrophages [1, 2]. Polymorphisms affecting genes encoding cytokines such as IFN-γ and tumour necrosis factor (TNF)-α as well as other immune mediators have been associated with increased susceptibility to tuberculosis (TB) in different populations [3–7]. Additionally, conditions that significantly impair cellular immune responses, such as HIV infection, increase the risk of developing active TB [8, 9]. Our

* Author for correspondence: M. A. Huaman, MD, MSc, Assistant Professor of Medicine, Division of Infectious Diseases, University of Kentucky, 740 South Limestone, K512, Lexington, KY 40536, USA.
(Email: moises.huaman@uky.edu)

group and others have previously published work that shows that otherwise healthy individuals who develop TB, particularly extrapulmonary disease, have subtle defects in both innate and cellular immune responses: lower CD4+ lymphocytes, lower basal cytokine production, and higher regulatory T cells [10–12].

Immunity to other intracellular bacterial infections (ICBIs) is mediated by host responses similar to those observed in *M. tuberculosis* infection [13–16]. Case reports of co-infection with TB and *Salmonella* spp., *Listeria monocytogenes*, or *Chlamydia* spp. are described in the literature [17–21]; however, larger population-based association studies have not been performed. In order to explore these possible associations, we conducted a population-based study in Tennessee, USA aimed at comparing the incidences of five reportable ICBIs (*Chlamydia trachomatis, Salmonella* spp., *Shigella* spp., *Yersinia* spp., *Listeria monocytogenes*) in persons who developed TB during the study period *vs.* the general population. We hypothesized that ICBIs would be more frequent in the TB group.

METHODS

We identified all cases of TB reported to the Tennessee Department of Health (TDH) from 1 January 2000 to 31 December 2011. All cases of *C. trachomatis, Salmonella* spp., *Shigella* spp., *L. monocytogenes*, and *Yersinia* spp. reported to the TDH during the same 12-year period were also identified.

Cases of *Salmonella* spp., *Shigella* spp., *Yersinia* spp., and *L. monocytogenes* were identified through the Foodborne Diseases Active Surveillance Network (FoodNet), a multistate population-based surveillance system for laboratory-confirmed foodborne infections [22]. Cases of *C. trachomatis* were identified through the TDH HIV/STD prevention programme, which captures surveillance data from patients seeking care at both private and health department clinics [23]. Cases of TB were identified through the Tennessee Tuberculosis Control Program. TB cases were verified as defined by the Centers of Disease Control and Prevention: (1) isolation of *M. tuberculosis* from a clinical specimen, (2) a positive stain for acid-fast bacilli in a clinical specimen, (3) clinical diagnosis, or (4) provider diagnosis [24]. Demographic characteristics of the population in Tennessee and additional information about completeness of reporting of TB and the other ICBIs are given in the Supplementary material. We have previously published detailed information on socio-demographic factors of TB cases reported in Tennessee [25].

Personal identifiers common to the FoodNet, HIV/STD, and TB surveillance systems were used to link TB cases with *C. trachomatis, Salmonella* spp., *Shigella* spp., *L. monocytogenes*, and *Yersinia* spp. cases. The final data-matching algorithm included soundex of last name and first name followed by exact match of month and year of birth. Soundex was used to increase the sensitivity of our data linkage by identifying true matches with minor typographical errors [26]. Matches with discordant day of birth were verified by the investigators to determine if they were true matches.

Clinical and demographic data were obtained when patients were diagnosed with these infections. For our analysis, the following variables were included: age (as a continuous variable and in 10-year age groups), sex, race (African American and non-African American), and ethnicity (Hispanic and non-Hispanic). Foreign birth and HIV status were only available for TB cases. For secondary analyses, TB cases were grouped into two categories: (1) pulmonary tuberculosis (PTB), which included cases of pulmonary disease with no extrapulmonary involvement, or (2) extrapulmonary tuberculosis (EPTB) which included cases of *M. tuberculosis* disease of any site other than the pulmonary parenchyma. Cases with both pulmonary and extrapulmonary involvement were classified as EPTB.

Demographic characteristics of the population of residents living in Tennessee were obtained from US census data [27]. Information was obtained for the same 12-year study period, including age, sex, race and ethnicity.

The study protocol was approved by the institutional review boards of the TDH and Vanderbilt University.

Statistical analysis

Incidences of ICBIs in the TB group were calculated for each pathogen by dividing the total number of cases of each ICBI among persons who developed TB during the study period by the cumulative number of person-years for people who developed TB in Tennessee from 2000 to 2011. For our analysis, each case of TB contributed 12 person-years unless date of birth occurred after the initiation of the study or death predated the end of the study period. Deaths in the TB group were verified by linking TB cases to

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Tennessee death certificates. Also, the number of person-years contributed by non-US born immigrants with TB was adjusted based on their date of arrival in the USA. Incidences of ICBIs in the Tennessee population were calculated for each pathogen by dividing the total number of cases of each ICBI during the study period by the cumulative annual estimates of the mid-year Tennessee population from 2000 to 2011 based on US census data. Crude incidence rates were calculated per 100 000 person-years. To compare the rates of ICBIs in the TB group and the Tennessee population, crude incidence rate ratios (cIRRs) and 95% confidence intervals (CIs) were calculated using negative binomial regression. We estimated that we would have about 80% power to detect IRRs of 1·25, 1·27, 2·5, and 3·4 for the combined ICBIs, *C. trachomatis, Salmonella* spp., and *Shigella* spp., respectively.

To calculate incidence rates and IRRs adjusted for age, sex, race and ethnicity, a cohort estimating the demographic characteristics of the Tennessee population from 2000 to 2011 was created. US census data contain the number of Tennessee residents, per year, in each of 72 categories corresponding to all possible combinations of sex, race (African American and non-African American), ethnicity (Hispanic and non-Hispanic), and 10-year age group. The average number of persons per year for each category was calculated from this information. The estimated Tennessee cohort was then established by transforming the number of persons in each category into observations in a master dataset; each observation contributing 12 person-years of follow-up in its respective category (Supplementary Fig. S1). Each case of ICBI was then inserted into its respective category replacing an observation. Finally, the TB dataset was added to this master dataset. Multivariable negative binomial regression analyses were used to calculate adjusted IRRs (aIRRs) and 95% CIs [28].

Missing race and ethnicity data among persons with TB and/or ICBIs was handled using a multiple imputation model [29]. Stata software version 12.0 (StataCorp, USA) was used for all data analyses. All *P* values are two-sided.

RESULTS

The average annual population of Tennessee for the study period was 6 048 239 persons. The median age was 37 years. Regarding the population, 48·7% were male, 80% were white, 17% were African American, and 3·6% were Hispanic.

Table 1 describes the demographic characteristics of the TB cases and other ICBIs. There were 3214 verified TB cases reported to TDH during the study period. Of these, 2380 (74%) persons had PTB and 834 (26%) had EPTB. Among TB cases, 741 (23%) persons were non-US born, 305 (9%) were infected with HIV-1 at the time of TB diagnosis whereas 2229 (72%) were not; 610 (19%) had unknown HIV status. There were 268 351 *C. trachomatis* cases, 9909 *Salmonella* spp. cases, 4349 *Shigella* spp. cases, 239 *Yersinia* spp. cases, and 152 *L. monocytogenes* cases reported to TDH during the study period. *Shigella* spp. and *Yersinia* spp. predominantly affected children and young adults whereas *L. monocytogenes* mostly affected elderly persons. Infections with *M. tuberculosis, C. trachomatis*, and *Yersinia* spp. were more frequently diagnosed in African Americans compared to non-African Americans in Tennessee ($P < 0·01$).

The annual incidence rates of ICBIs in the TB group and in the Tennessee population are shown in Figure 1. The crude and adjusted incidence rates and IRRs are shown in Table 2. Overall, persons who developed TB were not at increased risk of ICBIs compared to the Tennessee population (cIRR for all ICBIs combined, 0·92, 95% CI 0·76–1·1; aIRR 0·87, 95% CI 0·71–1·06).

There were 112 *C. trachomatis* infections in 80 of the 3214 TB cases during the study period (339·6/ 100 000 person-years). This rate was not significantly different from the overall *C. trachomatis* infection rate in Tennessee (369·7/ 100 000 person-years; cIRR 0·92, 95% CI 0·76–1·11; aIRR, 0·85. 95% CI 0·69–1·05). The analysis of rates was then restricted to persons aged between 10 and 40 years as this group accounted for 97% of all cases of *C. trachomatis* and again, there was no significant increase in the rate of *C. trachomatis* in persons with TB compared to the Tennessee population (1013 *vs.* 877/ 100 000 person-years, respectively; cIRR 1·15, 95% CI 0·94–1·4; aIRR 0·84, 95% CI 0·68–1·05).

In order to assess the potential direct effects of a recent TB diagnosis or anti-TB treatment on the rates of *C. trachomatis*, we also calculated and compared the rates of *C. trachomatis* infection after a recent diagnosis of TB. We looked at the first year post-TB diagnosis because anti-TB treatment requires at least 6 months and may be extended to 9–12 months for skeletal and other EPTB cases, or if suboptimal regimens

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Table 1. *Demographic characteristics of persons with tuberculosis and other infections due to intracellular bacteria in Tennessee, 2000–2011*

Characteristic	*Mycobacterium tuberculosis*	*Chlamydia trachomatis*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterolitica*	*Listeria monocytogenes*
No. of cases	3214	268 351	9909	4349	239	152
Age*	47·9 (32–66)	21·1 (19–25)	21·6 (3–51)	6·4 (3–14)	1·1 (.5–24)	61·3 (24–72)
Male sex	2129 (66)	71 565 (27)	4701 (48)	1926 (45)	115 (49)	72 (47)
Race						
African American	1326 (41)	143 429 (54)	1012 (10)	995 (23)	77 (32)	11 (7)
White	1267 (39)	90 878 (34)	5001 (51)	1743 (40)	73 (31)	88 (58)
Asian	220 (7)	414 (1)	43 (0·4)	23 (0·5)	13 (5)	2 (1)
Other	17 (0·5)	2,244 (1)	21 (0·2)	16 (0·4)	0	1 (0·6)
Unknown	13 (0·4)	31 386 (12)	3832 (38)	1572 (36)	76 (32)	50 (33)
Ethnicity						
Hispanic†	371 (12)	8864 (3)	180 (2)	138 (6)	5 (4)	6 (4)
Non-Hispanic	2843 (88)	233 890 (87)	5069 (52)	2218 (52)	134 (56)	89 (59)
Unknown	0	25 597 (10)	4579 (46)	1903 (44)	100 (42)	57 (37)

* Age is given as median in years and interquartile range. Other variables are presented as frequency (proportion).
† Hispanic origin is also considered as a race in the Tennessee Department of Health tuberculosis records.

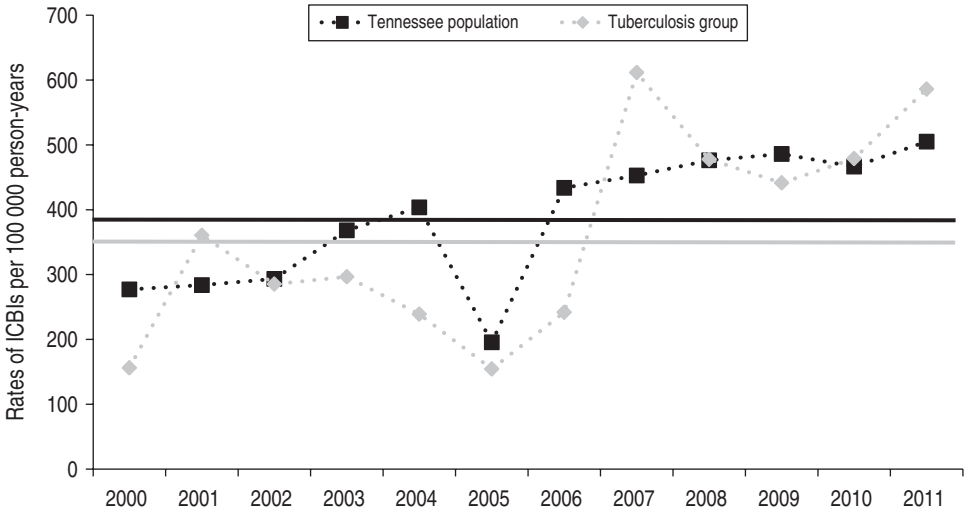

Fig. 1. Annual incidence rates of intracellular bacterial infections (ICBIs) per 100 000 person-years. The black squares (■) indicate the rates of ICBIs in the Tennessee population. The grey diamonds (◆) indicate the rates of ICBIs in the tuberculosis (TB) group. The solid black line (—) indicates the average rate of ICBIs in the Tennessee population for the study period. The solid grey line (—) indicates the average rate of ICBIs in the TB group for the study period.

are used. Overall, 54 (48%) of the 112 *C. trachomatis* events occurred after the diagnosis of TB, but only two cases occurred during the first year post-TB diagnosis (incidence rate 70·0/ 100 000 person-years). This rate was significantly lower than the average rate of *C. trachomatis* in the Tennessee population (cIRR 0·19, 95% CI 0·05–0·76; aIRR 0·17, 95% CI 0·04–0·70).

The rates of *C. trachomatis* infection in EPTB *vs.* PTB were not significantly different after adjusting for demographics (455·6 *vs.* 299·0/ 100 000 person-years, respectively; cIRR 1·52, 95% CI 1·02–2·27; aIRR 0·84, 95% CI 0·54–1·28), and did not materially change after introducing HIV status into the adjusted analysis ($n = 2604$ with known HIV status; IRR 0·77, 95% CI 0·48–1·22). In addition, no significant difference was found when comparing the rate of *C. trachomatis* infection in EPTB to the overall Tennessee rate (aIRR 0·83, 95% CI 0·58–1·18).

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Table 2. *Crude and adjusted incidence rates and incidence rate ratios of infections by intracellular bacteria in persons with tuberculosis, and all Tennessee residents, 2000–2011.*

	TB group* (32 980 person-years)		TN population (72 578 868 person-years)		Incidence rate ratios			
	Cases	Incidence†	Cases	Incidence†	Crude IRR	95% CI	Adjusted IRR‡	95% CI
Chlamydia trachomatis	112	339·6	268 351	369·7	0·92	0·76–1·11	0·85	0·69–1·05
Salmonella spp.	6	18·2	9909	13·6	1·33	0·60–2·97	1·69	0·76–3·76
Shigella spp.	0	0	4349	6·0	–		–	
Yersinia spp.	0	0	239	0·33	–		–	
Listeria monocytogenes	0	0	152	0·21	–		–	
All ICBIs	118	357·8	283 000	389·9	0·92	0·76–1·10	0·87	0·71–1·06

IRR, Incidence rate ratio; CI, confidence interval; ICBIs, intracellular bacterial infections.
* The incidence rate of tuberculosis in the Tennessee population was 4·4/100 000 person-years for the study period.
† Incidence rate per 100 000 person-years.
‡ Incidence rate ratio adjusted for age, sex, race, and ethnicity.

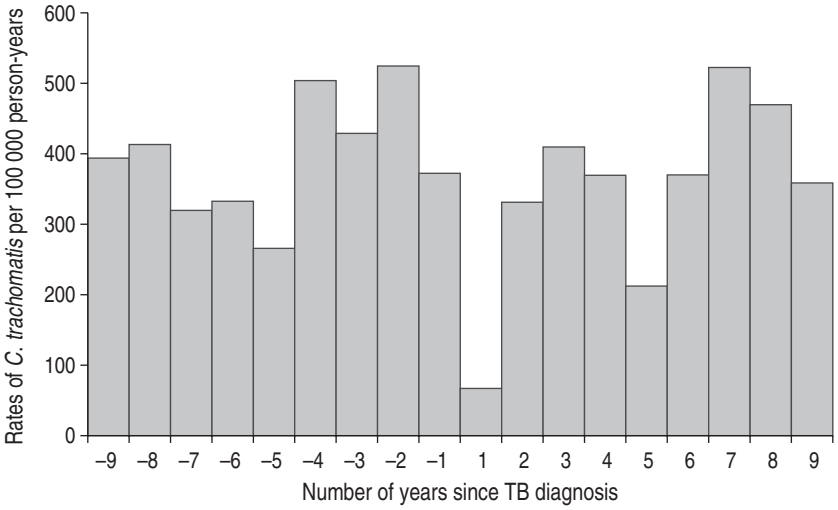

Fig. 2. Incidence rates of *Chlamydia trachomatis* infection per 100 000 person-years in the tuberculosis (TB) group. Rates are presented relative to the number of years elapsed between the diagnosis of TB and the diagnosis of *C. trachomatis* infection.

There were six *Salmonella* spp. infections in six of the 3214 TB cases during the study period. The incidence rate of *Salmonella* spp. in the TB group was 18·2/ 100 000 person-years, compared to 13·7/ 100 000 person-years in Tennessee (cIRR 1·33, 95% CI 0·60–2·97; aIRR 1·69, 95% CI 0·76–3·76). All six *Salmonella* spp. cases were co-infected with HIV and only one case occurred after the diagnosis of TB.

Five (83%) of the six *Salmonella* spp. infections in the TB group occurred in EPTB patients. Thus EPTB was associated with a higher rate of *Salmonella* spp. infection compared to PTB (58·4 *vs.* 4·1/ 100 000 person-years; cIRR 14·3, 95% CI 1·67–122). Compared to the Tennessee population, the rate of *Salmonella* spp. infection remained higher in the EPTB group (aIRR 5·1, 95% CI 2·1–12·2). There were no cases of *Shigella* spp., *Y. enterocolitica*, or *L. monocytogenes* in the TB group.

We found no clustering of *C. trachomatis* infections relative to the number of years since TB diagnosis ($P = 0·65$, Fig. 2). Clustering of other ICBIs relative to TB episodes could not be analysed due to the small number of the other ICBI cases.

In order to assess for possible heterogeneity with respect to the reporting site, we conducted separate analyses of IRRs for Shelby County and Davidson

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County as these two counties include the largest urban centres in Tennessee (Memphis and Nashville, respectively) and therefore pathogen exposure may not be comparable to the other counties in Tennessee. The IRRs in Shelby County and Davidson County were similar to the IRRs obtained for the entire state of Tennessee (data not shown).

DISCUSSION

In this large population-based study conducted in Tennessee, we found that TB was not associated with an increased risk of infections due to other intracellular bacteria. In fact, our results found a significantly decreased incidence of *C. trachomatis* infections within the first year post-TB diagnosis.

To our knowledge, this is the first study to explore the association between TB and other ICBIs in a population-based setting. Case series, animal models and immunogenetic studies have found that alterations in the expression of a variety of host genes encoding factors implicated in the immune responses to *M. tuberculosis* are also associated with an increased susceptibility to severe infections caused by taxonomically distant ICB [30, 31]. Examples include point mutations that lead to impaired function of key components of the IFN-γ and IL-12 signalling pathway [32, 33]. Moreover, gene mutations in the TLR-2 pathway have been found in persons with *M. tuberculosis* and other ICBIs [3, 34]. Although severe primary immunodeficiencies are often diagnosed in childhood and are associated with increased mortality, subtle immune defects such as low-level idiopathic CD4+ T cell lymphocytopenia or impaired IFN-γ mediated responses have been identified which may be diagnosed during adulthood or not formally recognized at all during a person's lifetime [35]. We hypothesized that the development of TB could be a marker of a subtle immne defect, that may increase the risk for other ICBIs of public health importance. However, our results do not support the hypothesis that such a defect is solely responsible for increased susceptibility to other ICBIs. Other factors such as exposure risk and pathogen-specific related factors may be of higher importance for determining the dynamics of TB and these other ICBIs at a population level, even in settings of low TB burden such as Tennessee.

EPTB was linked to a higher rate of *Salmonella* spp. infections compared to PTB and the Tennessee population. However, these associations were confounded by HIV infection as all patients with *Salmonella* spp. and TB were co-infected with HIV. Although HIV/AIDS substantially increases the risk of *Salmonella* spp. infection, particularly invasive non-typhoidal disease [36], it is unclear if non-HIV-mediated immune defects seen in persons with EPTB could have contributed to this increased number of *Salmonella* spp. infections in the EPTB group. Studies have shown lower CD4+ lymphocyte counts, decreased cytokine production and higher frequency of T regulatory lymphocytes in persons with prior EPTB compared to PTB, in the absence of HIV infection [10–12]. Therefore, larger studies to further characterize the possible association between EPTB and *Salmonella* spp. infections while controlling for HIV status may be considered.

The completeness of reporting for ICBIs in the TB group might be higher compared to the general population during the first year post-TB diagnosis, as patients in Tennessee undergo directly observed therapy (DOT) for the treatment of TB and are closely monitored by the health department. This could artificially increase the rates of ICBIs in the TB group due to increased exposure to healthcare during the year following the diagnosis of TB. In contrast, we found that among person who developed TB, there was a significantly lower risk of *C. trachomatis* infection within the first year post-TB diagnosis. This suggests that there may be 'protective' effects of a recent TB diagnosis or anti-TB treatment on *C. trachomatis.* For instance, there could be decreased exposure to sexually transmitted diseases during TB treatment, perhaps due to confinement during the contagious period, stigma associated with TB, or feeling too ill to be engaged in sexual activity [37, 38]. Also, *in vitro* and *in vivo* studies have shown that rifamycins such as rifampin have activity against *C. trachomatis*, so their use in anti-TB therapy may also prevent *C. trachomatis* infection [39, 40]. This could have potential public health implications for preventing this disease in high-risk groups where recurrent *C. trachomatis* infection, a major cause of pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain and infertility, is common [41, 42]. Alternatively, immunological responses against *M. tuberculosis* may have a partially protective effect on *C. trachomatis* infections, mediated by macrophage activation. This is supported by immunoepidemiological studies showing that higher production of a macrophage-stimulating factor such as IFN-γ is associated with protection against *C. trachomatis* infection and pelvic inflammatory disease [43, 44]. In addition, mice immunized with attenuated mycobacterial

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cells become partially resistant to challenge with *L. monocytogenes*, highlighting the potential role of macrophage activation on cross-species protection [45, 46].

This study has some limitations. Because we do not have longitudinal data on all persons in Tennessee over the 12-year period, we had to make several simplifying assumptions to estimate IRRs. For example, out-of-state migration/immigration was assumed to be negligible. The data-matching algorithm to identify persons who developed TB and other ICBIs could have missed some cases. In addition, although US Census data allowed us to adjust for age, sex, race, and ethnicity, other demographic and socioeconomic factors could be confounding observed relationships (or lack thereof) between TB and ICBIs that we were unable to account for in our analyses. Similarly, data on potential confounders such as HIV status, history of diabetes mellitus, cancer or use of immunosuppressive drugs were not available for the Tennessee population or the ICBI cases. These and other conditions that may significantly affect the host immune system should be included in future studies assessing the interplay between TB and other infections. Persons with cellular immunodeficiencies (i.e. T and B cell) are at increased risk for certain viral infections. Most viral infections are not reportable diseases and thus we were unable to assess whether they were more common in persons with TB. Given that this was a registry-based study, we used IRRs instead of relative risks (RRs) to compare the burden of ICBIs in the TB group *vs.* the general population. Although IRRs include both exposed (TB) and unexposed (non-TB) groups in the general population, IRRs approximate well the RRs in a setting like ours where the prevalence of the exposed group (TB) is low in the general population [47]. Although we had sufficient power to detect IRRs of ~1·25 for any ICBIs and *C. trachomatis*, we were under-powered to detect reasonably sized IRRs for the other ICBIs. Finally, we were unable to control for the fact that patients with known immunosuppression may be receiving antibiotic prophylaxis (e.g. HIV-infected persons may be taking prophylactic trimethoprim-sulfamethoxazole) and this could affect the incidence of ICBIs.

In conclusion, we did not find an association between TB and an increased risk of infections due to other intracellular bacteria. Our findings do not support the hypothesis that underlying subtle immune defects in persons who develop TB are sufficiently broad to confer increased susceptibility to other ICBIs at the population level. In fact, fewer *C. trachomatis* infections were observed within the first year after TB diagnosis. Reasons for this association, including possible confounders and potential mechanisms of protection, warrant further investigation.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268814002131.

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DECLARATION OF INTEREST

None.

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