National Surveillance for Severe Adverse Events Associated with Treatment of Latent Tuberculosis Infection

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Contact Information

Lilia P. Manangan, RN, MPH

Project Officer

Epidemiologist, Surveillance Team
Surveillance, Epidemiology and Outbreak Investigations Branch
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
1600 Clifton Road NE, Mailstop E-10
Atlanta, GA 30333
Voice: (404) 639-8401
Fax: (404) 639-8959
LManangan@cdc.gov

NATIONAL SURVEILLANCE FOR SEVERE ADVERSE EVENTS ASSOCIATED WITH TREATMENT OF LATENT TUBERCULOSIS INFECTION

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A. Justification

1. Circumstances Making the Collection of Information Necessary

Between October 2000 and October 2007, 79 patients receiving treatment for Latent TB Infection (LTBI) were reported to the Division of Tuberculosis Elimination (DTBE), Centers for Disease Control and Prevention (CDC) with severe adverse events to their medications (s). A severe adverse event is defined as a drug-related reaction resulting in hospitalization or death of a person receiving treatment for LTBI. Deaths reported among persons with LTBI included, 2 of 50 persons who were on the recommended two-month regimen of rifampin and pyrazinamide (RZ); 9 of 22 treated with isoniazid alone, and 2 of 3 patients on other regimens (e.g., pyrazinamide and ethambutol). Severe adverse events such as hospitalizations, liver transplants, and death related to treatment of LTBI continue to be reported to DTBE.

In order to determine risk factors and to monitor trends of severe adverse events related to the treatment of LTBI, CDC requests approval for information collection through the National Surveillance for Severe Adverse Events Associated with Treatment of LTBI. These reports are from healthcare providers and health departments (local/state/territorial) from any of the 60 reporting areas for the National TB Surveillance System (NTSS). CDC currently conducts and

maintains NTSS pursuant to the provisions of Section 301 (a) of the Public Service Act [42 U.S.C. 241] and Section 306 of the Public Service Act [42 U.S.C. 241 (a)] which also authorizes this proposed information collection (Attachment 1).

In compliance with the recommendations of the Institute of Medicine (IOM), Ending Neglect: The Elimination of Tuberculosis in the United States towards reaching the Healthy People (HP) 2010 objective, CDC is detecting and treating latent TB infection (LTBI) through targeted testing and administration of LTBI treatment to prevent transmission. Persons with LTBI are at highest risk for progression from latent infection to TB disease. However, with the increased number of persons with LTBI who will be treated with the recommended regimen of antibiotics, we anticipate that severe adverse events will occur more frequently.

2. Purpose of Use of the Information Collection

Severe adverse events to TB treatment are rare but recently recognized as a catastrophic medical phenomenon. We need to know who is affected, how often this occurs and, whether there are personal risk factors that contribute to severity of adverse reactions. Without this information, we will not be able to recognize which anti-tuberculosis drug (s) are more likely to cause severe adverse reactions and how

to change the antibiotic combinations used to treat persons with LTBI. Proper antibiotic regimens are crucial in the elimination of TB in the U.S.

The purpose of this information collection request is to determine the annual number and trends of severe adverse events associated with treatment of LTBI and identify common characteristics of patients with severe adverse events during treatment of LTBI. The collected data will be used to guide the revision of the TB treatment protocols in order to prevent severe adverse events associated with treatment of LTBI. CDC will use the information from all investigations to monitor trends in LTBI detection and compile the nature of severe adverse events to treatment regimens associating patient characteristics, clinical events and the treatment regimens that the patient has been required to take. CDC will use the cumulated data on LTBI treatment and severe adverse events to convene stakeholders and recommend revisions of current LTBI treatment regimens based on patient’s medical history and the perceived risk of severe adverse events. Concurrent HIV infections will be of particular interest to CDC in evaluating treatment options to reduce or eliminate severe adverse events to LTBI.

Information collection will be initiated when a health department is notified of a person hospitalized with severe adverse reactions to the medications prescribed to treat

LTBI. The investigations may be conducted by the reporting health department with or without CDC staff at the local site. All investigators will follow the procedures described in “Guidelines to Investigate Reports of Severe Adverse Events to LTBI Treatment” (Attachment 5) and use the Adverse Events to LTBI Treatment (AELT) form developed specifically for these investigations (Attachment 4). CDC will participate only when invited by local or state health departments. Details of data collection are in Section B.2.

3. Use of Improved Information Technology and Burden Reduction

Because we expect to respond to only 4 reported severe adverse events each year, the use of paper forms is most suited for this small but important information collection. The information collected during each report will be collected from medical records, treatment records, and abstractions from the records at the facility where the case has been admitted during the severe adverse event. Information technology can partially reduce the burden of the physicians and the medical clerk who will be contributing clinical information from the medical charts, if the facility where the patient has been admitted uses electronic health record systems.

At CDC, we will maintain all of the information collected in a Microsoft Access database. At the local level, paper forms also will be used to collect data which will be submitted to CDC. Data will be obtained by reviewing medical records and interviewing healthcare providers. The Guidelines for investigating adverse events to LTBI treatment (Attachment 5) will provide instructions to conduct the investigations and the information to be included in the Adverse Events due to Latent Tuberculosis form (AELT, Attachment 5)

If requested by the health departments, or the physician, CDC will conduct a site visit to thoroughly investigate each case of severe adverse reaction to LTBI treatment.

4. Efforts to Identify Duplication and Use of Similar Information

The MEDWATCH system implemented by the Food and Drug Administration (FDA) Safety Information and Adverse Event Reporting Program, is a passive surveillance of adverse events related to individual drugs and products. However, the data collected by FDA do not include relevant patient medical history nor is associated with medical conditions of public health priority.

Through literature searches, attendance at national TB meetings/conferences, and ongoing consultations with TB

experts nationwide, CDC has determined that the data collected by the National Surveillance for Severe Adverse Events Associated with Treatment of Latent Tuberculosis Infection provide the sole source of comprehensive national statistics and are not available from any other source within the federal government or from non-federal sources.

5. Impact on Small Businesses or Other Small Entities

There will be no impact on small businesses. Physicians who report the case to the local health department are required by state and national regulation to report tuberculosis. Their participation in providing the information is part of their regular duties. No additional tasks are required of the physicians or the medical clerks in the hospital.

6. Consequences of Collecting Information Less Frequently

Information collection is minimal because it is initiated only when CDC receives a report of severe adverse event related to treatment of LTBI.

7. Special Circumstances Relating to the guidelines of 5 CFR 1320.5

Collection of data is conducted in a manner consistent with the guidelines in 5 CFR 1320.5 . An excerpt from the authorization that supports the data collection follows: “An

agency shall not conduct or sponsor a collection of information unless, in advance of the adoption or revision of the collection of information—the agency has—

(i) Conducted the review required in §1320.8;

(ii) Evaluated the public comments received under §1320.8(d) and §1320.11;

(iii) Submitted to the Director, in accordance with such procedures and in such form as OMB may specify."

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

Notification of the request for OMB clearance was published in the Federal Register on December 14, 2006, Volume 71, Number 240 (Attachment 2). CDC received one public comment about our immigration laws not being enforced and that "medicines that kill should be taken off the market." CDC responded in a letter explaining that CDC is collaborating with agencies responsible for immigration screening and for regulating drugs. (Attachment 2).

A previous 60 day notice was published in the Federal Register on November 29, 2004, Volume 69, Number 228, Page 69372-69373 (Attachment 3). CDC received one public comment on this information collection request. The requestor commented about CDC underestimating the burden of the data collection form on the local and state health departments.

CDC responded by providing an explanation and changing the estimated burden hours from one hour per case to eight hours per case (Attachment 3).

CDC is guided by extramural TB specialists and CDC stakeholders in TB elimination. These groups have assisted in the design of the Severe Adverse Events Associated with Treatment for Latent Tuberculosis Infection including the adverse events related to treatment of LTBI (AELT) data collection form (Attachment 4). The development and implementation of this investigation and reporting is supported by the National Tuberculosis Controllers Association (NTCA) and the detection of persons with severe adverse events to LTBI treatment is a collaborative effort by CDC, NTCA, state and city TB controllers.

9. Explanation of Any Payment or Gift to Respondents

Respondents (physicians, nurses and medical clerks) will not receive gifts nor be paid for completing the case report form.

10. Assurance of Confidentiality Provided to Respondents

Data from the local site will be safeguarded as described in the Privacy System of Records Notice 0920-0136, *Epidemiologic Studies and Surveillance of Disease Problems*. Consent from the patients or patient’s guardians and the healthcare providers will be obtained before the interview to

obtain data on the adverse events (Attachment 7). Name and address of the patient will be retained by the reporting area. The local project officer will assign a unique identification number to each case which excludes personal identifiers (e.g., social security number, date of birth) and is used to facilitate communication between CDC and a reporting area when needed. The patient masking procedure will be the same even if CDC is invited to help the health jurisdiction complete the investigations. Interviews conducted by CDC personnel will also use the unique case number. All hard copy case reports and associated documents will be kept in a locked cabinet by the local and CDC project officers for a period of 3 years. Access to the cabinet will be limited to the project officer.

The Access database maintained by the CDC project officer will be password protected with only authorized DTBE staff having access to the file. Line listed data in hard copy form, when temporarily needed for data management purposes, also are kept in locked cabinet by the CDC project officer for a period of 3 years.

This investigation protocol has been determined by the Associate Director of Science, National Center for HIV, STD, and TB Prevention, CDC as routine surveillance and also post marketing surveillance and as such is not research (Attachment 6).

11. Justification for Sensitive Questions

Case investigations of persons with severe adverse events to LTBI treatment will include sensitive issues such as:

a) HIV status: People with HIV-infection are at extremely high risk for developing active TB once infected and have contributed to the resurgence of TB in the late 1980s and early 1990s. We will use the information from the investigations of persons with severe adverse events to LTBI treatment to monitor the impact of the HIV/AIDS epidemic on TB morbidity, increase in drug-resistant TB, and potential interactions of AIDS medications with LTBI treatment regimens.

b) Drug use (injecting, non-injecting) and excess alcohol use: Non-adherence to the prescribed regimen of anti TB medications is one of the major reasons for acquiring drug-resistant TB and persons who use illicit drugs are most note-worthy for non-compliance to prescribed treatments. CDC will also study whether TB patients that abuse alcohol and/or illicit drugs have comparable or different rates of severe adverse events due to LTBI treatments.

c) Race/ethnicity – TB incidence rates among minority race groups is very high. By knowing the trends in severe adverse events by race/ ethnicity, CDC could develop further activities among the stakeholders that serve specific race/

ethnic groups to communicate health information messages as we craft these.

12. Estimates of Annualized Burden Hours and Costs

From January 1, 2004 through October, 2007, 60 reporting areas (50 states, the District of Columbia, New York City, Puerto Rico, and 7 jurisdictions in the Pacific and Caribbean) reported eight severe adverse events associated with treatment of LTBI were reported to the CDC, an average of 4 cases per year. We anticipate that a single physician, one nurse, and one medical clerk will be involved in collating the information needed by CDC. Each of the three types of respondents (physicians, nurses, medical clerks) provide uniquely different information in a single Adverse Events Latent TB (AELT) case form.

The physicians will provide medical information from the admission such as treatment, laboratory or pathology findings in the appropriate section of the AELT form. We anticipate that each physician will need three hours for each response/case. Each nurse will spend four hours per case, completing the demographic, social, and medical history of the patient in the appropriate sections of the AELT form. The medical clerks will spend approximately one hour to abstract the patient information from the hospital’s medical records including laboratory findings and complete the AELT form.

We anticipate that the total burden for all 3 respondents to be eight hours per response (i.e. per case). The total burden

for all 3 health professionals, for 4 cases per year, is estimated to be 32 hours (4 x 8 hours).

12A. Estimated Annualized Burden

Type of Respondent	Form name	No. of Respondents	No. Reponses Per Respondent	Average Burden per Response (in hours)	Total Burden Hours
Physician	AELT	4	1	3	12
Nurses	AELT	4	1	4	16
Medical Clerk	AELT	4	1	1	4
Total					32

[+]AELT=adverse events related to latent TB infection

B. Estimate of annualized cost to respondents

The cost per person-hour is based on the mean hourly wage of medical clerk, nurse, and physician from the U.S. Department of Labor at http://www.bls.gov/oes/current/oes_nat.htm accessed on October 10, 2007. Reporting areas receive annual federal funds for TB control and surveillance through CDC cooperative agreements. In hospitals where the local or state health departments have contracts there is no cost to the respondents for providing the information. Private hospitals may choose to negotiate with the health department for payment which cannot be anticipated at this time.

12B Estimated Annualized Burden Costs

Type of Respondent	Form name	Total Burden Hours	Hourly Wage Rate*	Total Respondent Costs Responses Per Respondent
Physicians	AELT[+]	12	$72.04	$864.48
Nurses	AELT	16	$28.71	$459.36
Medical Clerk	AELT	4	$14.49	$ 57.96
Total**				$1381.80

[+]AELT= Adverse events to LTBI Treatment

13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no capital or maintenance costs to the respondent resulting from the collection of the information.

14. Annualized Cost to the Government

This project is an adjunct to NTSS which collects notifiable disease reports including TB, from 60 reporting areas in the United States and U.S. jurisdictions because it investigates unusual events among the persons reported to the NTSS with TB. The estimated annualized cost to the federal government for this project is partially derived from the NTSS.

Table A.14: Estimates of Annualized Costs to the Federal Government

Expense	Expense Explanation	

Type		Annual Costs (dollars)
Direct Costs to the Federal Government	CDC Project Officer (GS-14, .10 FTE) CDC Medical Officer(GS-15, .05 FTE) CDC Supervisory Epidemiologist (GS-14, .025 FTE) CDC Medical Officer (GS-15, .013 FTE)	$10,600 $ 5,300 $ 2,300 $ 3,000
	Cooperative agreement for investigations of severe adverse reactions to LTBI treatments	$ 1,382*
Travel	Anticipate 4 round-trip travels within US or its territories for two staff.	$ 16,000
Total		$38, 582

*Cost to the respondents (physicians, nurses, medical clerks) included in A.12B

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

A.16 – 1 Project Time Schedule

Activity	Time Schedule
Notification of respondents	1-2 months after OMB approval
Collect data on reported severe adverse events	3-30 months after OMB approval
Analysis	31-32 months after

	OMB approval
Dissemination of results	33-36 months after OMB approval

The AELT data will be included in DTBE materials for training and education of health care providers, the general public, and the media. Analyses on trends and associations of severe adverse events to LTBI treatment will be published in CDC's Morbidity and Mortality reports and peer-reviewed scientific journals.

17. Reason (s) Display of OMB Expiration Date is Inappropriate

Data collection forms will include OMB Expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions to certifications are being made.