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Population-Based Lupus Registries: Advancing Our Epidemiologic Understanding

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Introduction

Without a new medication approved for systemic lupus erythematosus (SLE) by the Food and Drug Administration in more than 40 years, there has been a recent flurry of research activity and clinical trials. However, a basic epidemiologic understanding of SLE, which is necessary to understand the full clinical spectrum and population burden, lags behind. Estimates of the incidence and prevalence of SLE in the US have varied widely and are outdated (Table 1). This is likely due to the use of different case definitions, limited sources for case ascertainment, small source populations, and different demographic groups targeted, as well as the protean characteristics of the disease, poor reliability of self-report, lack of reliability in diagnosis and coding in health system databases, and issues related to access to health care by high-risk populations. Estimates for other types of lupus (e.g., primary discoid lupus) are even less well defined.

Two ongoing population-based lupus registries are currently addressing many of these issues, using methods that take advantage of novel federal, state, and local partnerships. In keeping with the goals of the "National Arthritis Action Plan: A Public Health Strategy" (1), the Centers for Disease Control and Prevention (CDC) Arthritis Program in 2002 competitively funded small grants in the health departments of 3 states to plan a population-based registry to better define the incidence and prevalence of diagnosed lupus and to better characterize individuals with this disease. Areas with a population of more than 1 million and with a relatively large African American proportion were eligible. In 2003, state health departments in Georgia and Michigan along with their academic partners, Emory University and the University of Michigan, were competitively awarded funding to perform this research.

This article provides an overview of the methods used in these registries, focusing primarily on SLE and emphasizing aspects unique in the field of lupus epidemiology. We also report briefly on our progress and discuss future directions.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the CDC.

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Materials and Methods

The primary aim of the Georgia Lupus Registry and the Michigan Lupus Epidemiology and Surveillance Program is to determine the prevalence in 2002 and the incidence in 2002–2004 of diagnosed SLE in defined geographic areas: Fulton and Dekalb counties (Atlanta) in Georgia, and Wayne (Detroit) and Washtenaw (Ann Arbor) counties in Michigan.

Preregistration activities (2003–2004). A fundamental strategy for the success of the lupus registries is the partnership of the state health department with an academic counterpart. The state health department has the power to conduct public health surveillance and provides surveillance expertise. Because of its legal authority, the state health department is a "public health authority" under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR parts 160 and 164). Health care providers are allowed under the HIPAA Privacy Rule to provide protected health information, without written patient consent, to state health departments and their designated agents (45 CFR 164.512[b]). Collecting protected

Table 1. Major epidemiologic studies of incidence and prevalence rates in SLE in the US*

Author, year (ref.)	Study location	Total population at risk	Total no. of SLE cases	Survey years	Case ascertainment sources	Overall annual incidence per 100,000	Overall prevalence per 100,000
McCarty et al, 1995 (8)	Allegheny County, PA	1,336,449	269	1985–1990	Rheumatologists, hospitals, university database (SLE)	3.4	ND
Siegel et al, 1970 (9)	New York, NY and Jefferson County, AL	1,165,700 whites and African Americans	193	1956–1965	Hospital files	2.0	19.3
Fessel, 1974 (10)	San Francisco, CA	121,444 members of Kaiser Foundation Health Plan	74	1965–1973	Outpatient diagnoses from internists and dermatologists (SLE, discoid)	7.6	50.8
Michet et al, 1985 (11)	Rochester, MN	28,247 (1950) 56,447 (1980)	25	1950–1979	Community diagnostic retrieval system (SLE, ANA, LE cell, false-positive syphilis)	1.8	40.0
Hochberg, 1985 (12)	Baltimore, MD	Not given	302	1970–1977	Hospital discharge (SLE)	4.4	ND
Uramoto et al, 1999 (13)	Rochester, MN	106,470 (1990)	48	1950–1992	Community diagnostic retrieval system (SLE, ANA, LE cell, false-positive syphilis)	5.56	122
Walsh et al, 2001 (14)	Nogales, AZ	19,489 (92% Mexican Americans)	20	1997	Community referrals to lupus evaluation center, practice database search (SLE)	ND	94
Naleway et al, 2005 (15)	Rural Wisconsin	77,280 (97% whites)	117	1991–2001	Community clinic electronic records (SLE)	5.1	78.5
Ward, 2004 (16)	NHANES-III	Enriched sample of the US population (20,050)	40 self-report, 12 also receiving SLE medications	2000	Self-reported physician diagnosis from NHANES-III	ND	241 by self-report, 53.6 receiving SLE medications

* SLE = systemic lupus erythematosus; ND = not determined; ANA = antinuclear antibody; LE cell = lupus erythematosus cell; NHANES-III = Third National Health and Nutrition Examination Survey.

health information is needed to determine if diagnosed cases meet case definition criteria and to provide enough information to prevent duplicate entry of patients, because the same patient may be encountered in multiple facilities. Obtaining individual consent for case finding and medical record reviews would be prohibitively costly and time consuming, and result in severe underreporting and biased ascertainment. The academic partner provides the onsite expertise in lupus to conduct the registry. Therefore, the state health departments contracted with the academic partners (Emory University and the University of Michigan) to implement the CDC grant by managing the project and collecting the data. In addition, all pertinent local, university, state, and CDC Institutional Review Board reviews and approvals have been obtained.

Advisory committees comprised of regional leaders from academia and private practices were established early at each site to address potential roadblocks and to help finalize the methods. Representatives from hospital organizations, medical records departments, and patient

advocacy groups also participated. Outreach from the advisory committees to relevant specialty organizations and hospitals helped to maximize awareness and participation.

With CDC coordination, monthly conference calls, and consultation by a lupus epidemiology expert (CG) who had completed a similar population-based study of SLE incidence and prevalence using multiple sources of case ascertainment in the UK (2), a standard set of methods and data definitions was developed for both sites. The intent was to minimize methodologic differences between these 2 registries when comparing estimates, which is a common problem in comparing lupus estimates between other studies.

Case finding (registration methods, 2004 to present). To maximize ascertainment of potential cases, a broad range of case-finding sources are being used (Figure 1). Within each source, a search is made for SLE, discoid lupus, and selected conditions that may evolve into SLE or have related symptoms. Other lupus-related conditions such as primary antiphospholipid syndrome, neonatal lupus, drug-induced lupus, and primary nondiscoid cutaneous lupus are not being pursued at this time because of their lack of specific diagnostic codes and/or established classification criteria. Administrative databases at each source are queried for the International Classification of Diseases, Ninth Revision, Clinical Modification billing code 710.0 (SLE), as well as 695.4 (discoid lupus), 710.8 (other specified connective tissue disease), and 710.9 (unspecified connective tissue disease). Hospital-based laboratories and regional pathology laboratories are also queried for results that may identify patients with SLE or other related conditions (e.g., skin and renal biopsies). Efforts to obtain data from the larger commercial laboratories and the US Renal Data System database are currently underway (data have been obtained from LabCorp; data request is pending for Quest). Other unique databases such as the Veterans Administration data, Medicaid claims data, other state databases (mortality, hospital discharge), and electronic medical record systems are used as available.

Data abstraction. Once a potential case is identified, only confirmation of residency in a county of interest during the calendar period of interest is needed to initiate full abstraction of the various medical records. Abstractors are thoroughly trained and tested. They do not make an a priori assessment of the diagnosis, nor do they stop abstracting when any of the classification criteria for SLE are met. Both sites regularly assess the quality of data abstraction in a standard fashion by using a method of re-abstracting medical records. This is a significant improvement over previous studies.

Data elements. Personal identifiers are collected to prevent duplicate entry of patients. Detailed addresses are used to confirm county residency. More than 200 data elements with detailed definitions in a study glossary are potentially abstracted for each patient at each facility, with core data including all of the elements required for various

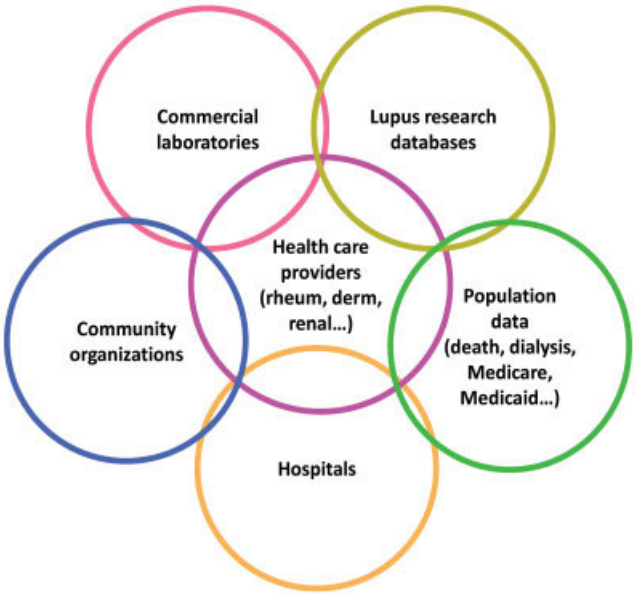

Figure 1. Sources of potential systemic lupus erythematosus cases.

SLE classification criteria, including the American College of Rheumatology (ACR) (3) and Boston weighted criteria (4). For each ACR criterion, the source of the data (reported by the patient or documented by the physician) and the earliest date of occurrence are also abstracted. Currently, the Systemic Lupus International Collaborating Clinics (SLICC) group is revising the ACR criteria. Each new element being evaluated by SLICC not currently in the ACR criteria was added to the original core data set.

Data analysis. Because abstraction of a potential case is triggered based on only 2 main criteria (potentially having SLE and documentation of residency in a county of interest during the calendar period of interest), the registry databases contain a broad spectrum of patients. Once classification criteria or other case definitions have been applied to the broad database, cases can be verified and demographic and disease subsets identified. Population denominators were obtained from official government sources. A capture–recapture analysis with confidence intervals will be performed to estimate the number of cases missed. Estimates of the incidence and prevalence for the entire spectrum of diagnosed SLE meeting standard classification criteria will be obtained using the largest population-based registries of whites and African Americans ever assembled.

Results

A snapshot of the status of abstracting at target facilities and practices (Table 2) and the numbers of diagnosed SLE cases meeting classification criteria are reported (Table 3), stratified by sex and race (African American and white). Numbers shown are for information only and should not be used to estimate incidence or prevalence rates.

Table 2. Status of abstracting at case source facilities in and near the study areas as of December 31, 2008

Facility	Total no.	No. completed or ongoing	Complete, %
Georgia			
Hospitals	19	17	89
Rheumatologists	34	25	74
Nephrologists	79	38	48
Dermatologists	103	21	20
Michigan			
Hospitals	46	20	43
Rheumatologists	67	44	66
Nephrologists	102	56	55
Dermatologists	89	31	35

Discussion

Epidemiology is the study of the distribution, determinants, and control of disease in populations. By identifying and counting people with lupus at these sites, more accurate estimates of incidence and prevalence rates will greatly improve our understanding of lupus and related diseases, its public health burden, and implications for health care planning. The CDC-funded effort to address the epidemiology of lupus in Georgia and Michigan is the most comprehensive of such efforts to date in the US. The size and scope of the active surveillance endeavors currently underway are designed to encompass the full spectrum of lupus, extending beyond the tertiary care setting. With ~3,000 lupus cases already registered, estimates will be more statistically precise than those previously available, and meaningful subset analyses will, for the first time, be feasible from a population-based setting.

Although previous epidemiologic studies of SLE in the US (Table 1) have all helped to advance our knowledge of the disease, from an epidemiologic perspective they were relatively limited because most were not truly population based or were relatively small in size (range 20–302 cases). Case ascertainment sources varied considerably, with some studies only reviewing hospital files, whereas others used different aspects of electronic records systems and/or laboratory tests or patient self-report. There was little systematic review of potential cases outside of hospitals and rheumatology offices. Classification criteria also varied, ranging from clinical suspicion with a suggestive histologic or immunologic finding (2) to various versions of the ACR classification criteria (1971, 1982, or the 1997 update) (3,5,6). Furthermore, different estimates were adjusted in different ways or not at all. Consequently, it became difficult to compare the different studies or to apply any of the results toward a credible national estimate.

The Georgia Lupus Registry and Michigan Lupus Epidemiology and Surveillance Program offer several advantages and strengths over previous efforts. They collect significant clinical information on each patient from a wide variety of case-finding sources without the limitations of obtaining individual consent, and should provide population-based estimates of incidence and prevalence for the full spectrum of diagnosed SLE and primary discoid lupus. Because the classification criteria for SLE may be in flux, the data elements provide flexibility in adapting to different case definitions, as well as potentially assessing those criteria. The large number of validated cases already gathered allows for greater power to look at differences between sex, race (African Americans versus whites), and age groups (childhood onset versus adult onset), and this will improve as case finding and abstracting is completed. Definitions of the core data set and methods between both states are essentially identical, allowing for comparability between the data sets. The large size of the registries will provide the best data yet for estimating the national burden of SLE among whites and African Americans.

The registries also have limitations. First, the data are retrospective and abstracted from medical records from known or suspected lupus patients that were not designed for epidemiologic purposes. These methods are not designed to capture undiagnosed lupus. Second, the fragmented system of health care in the US complicates public health surveillance efforts. Particularly for complex, noncommunicable diseases such as lupus, some relevant cases may fail to be captured. To mitigate this risk, we have designed a comprehensive, active surveillance system with numerous case-finding sources, and will apply capture–recapture analysis to estimate the degree of underascertainment that may have occurred (7,8). To reduce the risk of overdiagnosis, detailed quality control measures have been put in place to ensure that abstractors extract clinical features that are likely to be due to lupus and not to another disease process. Third, patients may migrate in and out of the catchment area for medical care or residency. Fourth, the methods outlined require significant effort and expense. Reproduction of such efforts may be limited by resources. Fifth, these registries do not include large subsets of other important racial/ethnic populations

Table 3. Current minimum estimates for systemic lupus erythematosus (SLE) in the ongoing lupus registries (as of December 31, 2008)

	Number of validated SLE patients, 2002–2004*
Georgia, overall†	1,362
Whites, total	261
Men	28
Women	233
African Americans, total	1,049
Men	103
Women	946
Michigan, overall‡	1,912
Whites, total	751
Men	84
Women	667
African Americans, total	1,046
Men	80
Women	966

* Meeting either ≥4 of 11 revised 1982 American College of Rheumatology (ACR) criteria or 3 ACR criteria with a final diagnosis of SLE by a rheumatologist.
† Fulton and Dekalb counties.
‡ Wayne and Washtenaw counties.

thought to potentially be of high risk for SLE in the US, particularly Hispanics, Asians, and American Indians/Alaska natives. Planning is currently underway to establish additional sites in areas that would better capture these persons and ultimately allow for a more comprehensive and generalizable national estimate to be formulated.

The methods outlined for the 2 registries can potentially be used for much more than determining incidence and prevalence of disease. They will allow a cross-sectional assessment of the association of a variety of factors, including socioeconomic factors and outcomes not systematically incorporated in other epidemiologic studies of lupus. Once completed, the registries logically will provide a well-defined cohort that could, with proper consent, be prospectively followed over time to address important issues with respect to disease progression and management.

The registries in Georgia and Michigan will greatly advance our epidemiologic knowledge of lupus in the US. They are a model of how government and academic partnerships can be leveraged to effectively ascertain a large number of cases from multiple sources to obtain reliable population estimates.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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