

Final Report of the Prevalence of Amyotrophic Lateral Sclerosis and Multiple Sclerosis and Ecologic Evaluation of Selected Environmental Factors in Southeastern Massachusetts

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Abstract

The purpose of this investigation was to (a) identify all persons with diagnoses of amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) living in Southeastern Massachusetts (all of Plymouth County plus Raynham and Weymouth) during the period 1998 through 2003; (b) calculate prevalence estimates for the study area and individual study communities; and (c) evaluate the geographic occurrence of these diseases in Southeastern Massachusetts, with specific focus on the areas surrounding the former South Weymouth Naval Air Station (SWNAS) and hazardous waste sites in Middleborough, to determine the likelihood that environmental factors may play a primary role in their occurrence. Any individual whose medical record indicated a diagnosis of ALS or MS before or during the surveillance period and who had a neurologist visit during the six-year period as a resident of the surveillance area was eligible for inclusion in the study. The primary sources of cases were neurologists and hospitals serving the study area.

The 1998-2003 prevalence of ALS in Southeastern Massachusetts, based on all verified diagnoses (i.e., all patients with a definite or probable ALS diagnosis according to the El Escorial World Federation of Neurology criteria), was estimated to be 3.4 cases per 100,000 population. When statistically contrasted with a comparison area outside of Massachusetts (Jefferson County Missouri: 3.9 per 100,000), the prevalence in Southeastern Massachusetts was determined not to be elevated. Further, the prevalence of ALS estimated for the US is 4-6 per 100,000. No cases of ALS among Middleborough residents were documented during 1998-2003. Ten cases of ALS were reported among residents of Abington, Rockland, and Weymouth. The numbers of cases were too small for meaningful statistical tests to be conducted, and residential information demonstrated that cases were geographically dispersed across the communities.

The prevalence of all verified cases of definite or probable MS in Southeastern Massachusetts for 1998-2003 was estimated to be 103 per 100,000 population. The 1998-2003 prevalence estimate for the three communities surrounding SWNAS (Abington, Rockland, and Weymouth) was 144 per 100,000. The two estimates were statistically significantly different from each other. Prevalence in northern latitudes of the US has been observed to generally range from 110 to 140 per 100,000.

A comparison population outside Massachusetts was selected to determine if the MS prevalence observed in Massachusetts was statistically significantly elevated. In order for the prevalence estimates to be compared with a comparison population, estimates needed to be compared for the same data collection period (1998-2001) so that any observed differences would not be affected by having a longer period for cases to be diagnosed in one of the areas. For 1998-2001, prevalence for the Southeastern Massachusetts study area was 91 per 100,000; prevalence for the SWNAS communities was 109 per 100,000; and prevalence for the comparison area (Independence, Missouri) was 115 per 100,000. None of these prevalence estimates were statistically significantly different from each other.

To further assess if the prevalence of MS was higher in areas closest to the SWNAS, statistical cluster detection methods were used and found a greater concentration of individuals diagnosed with MS living in communities abutting the SWNAS than elsewhere in the surveillance area. Importantly, however, the number of individuals with a diagnosis of MS did not increase in areas closest to the base. This suggested that the base was unlikely to have played a primary role in the prevalence.

For both ALS and MS, health professionals reported a number of cases for which medical records were incomplete and, therefore, could not be included in the reported prevalence estimate. In addition, patient advocacy groups reported a number of cases as having a diagnosis of MS, but these were not reported to the study by neurologists or hospitals. Thus, their medical records could not be reviewed and, therefore, they could not be included in the prevalence estimate. It is possible that some of these cases are valid ALS and MS diagnoses and, therefore, it was concluded that the true prevalence is likely somewhat greater than reported in both the study area and in the comparison population.

These observations underscore the need for broader disease surveillance efforts in order to obtain more precise estimates of the occurrence of these diseases. The statewide Massachusetts ALS Registry has adopted revised methods based on the lessons learned from this study and is now able to generate precise estimates of ALS prevalence across the state. In addition, a national ALS registry is currently being developed by ATSDR and should be able to provide valuable data on an annual basis as to whether Massachusetts' prevalence differs from

that of other states and the US as a whole. Regarding MS, the MDPH will work with CDC/ATSDR to explore the feasibility of developing an MS surveillance system.

1.0 Project Goal

The goal of this epidemiologic investigation was to determine the prevalence of amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) in 30 Southeastern Massachusetts communities and to evaluate the geographic occurrence of these diseases in relation to specific environmental sites of concern. More specifically, concerns regarding suspected elevations in the occurrence of ALS were expressed in the community of Middleborough, and residents who live in close proximity to the South Weymouth Naval Air Station (SWNAS) expressed concerns associated with the suspected elevations of MS. To accomplish this goal, the Massachusetts Department of Public Health (MDPH) developed a standardized case ascertainment methodology to estimate the prevalence of both ALS and MS in the study communities. The MDPH also evaluated the distribution of MS and ALS cases in relation to selected federal- and/or state-regulated hazardous waste sites in the surveillance area. The specific objectives of the project were:

- Objective 1: To provide an accurate estimate of the prevalence of ALS and MS in 30 communities of Southeastern Massachusetts over the six-year period 1998 through 2003; gathering case information through medical records obtained from neurologists serving the southeastern Massachusetts medical service area and MS and ALS medical clinics in Boston.
- Objective 2: To evaluate the extent of spatial clustering in the study area, including the distribution of cases in relation to specific sources of environmental contamination, including the South Weymouth Naval Air Station in Weymouth and hazardous waste sites in the Middleborough/Raynham area.
- Objective 3: To identify important components necessary to establish an ALS/MS surveillance system through the evaluation of case ascertainment completeness and reliability.
- Objective 4: To establish an ALS/MS Advisory Group for information exchange and collaboration during the course of the investigation.

2.0 Background

2.1 Amyotrophic Lateral Sclerosis

2.1.1 The Disease

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neuromuscular disease involving both upper and lower motor neurons. The causes of ALS (also known as Lou Gehrig's disease) are not fully understood. It is characterized by a degeneration of motor nerve cells in the brain and spinal cord, leading to muscle weakness. As the disease progresses, total paralysis and the inability to speak or swallow can result. For the vast majority of people with ALS, the mind and senses remain intact and unaffected. Symptoms include muscle weakness, with atrophy; twitching and cramping of muscles, especially those in the hands and feet; impairment of the use of the arms and legs; "thick speech" and difficulty in projecting the voice; and in more advanced stages, shortness of breath and difficulty in breathing and swallowing (ALS Association 2000). Its symptoms make it difficult to distinguish from other muscular atrophies and related forms of the disease, particularly for epidemiological studies (Roman 1996).

2.1.2 Types of ALS

The types of ALS include sporadic (classic), coexistent-sporadic, ALS-related syndromes, and ALS variants (Brook 1994). In the USA, 90% of ALS cases are sporadic while approximately 5-10% have a family history of ALS (Kamel et al. 2002; Armon et al. 1991). Beyond the genetic link, several major hypotheses exist about the pathogenesis of ALS. These include immunological factors, viral infection, and environmental toxins.

2.1.3 Epidemiology

ALS is estimated to affect some 18,000 people in the United States at any given time. The annual incidence is about 2 per 100,000 and prevalence is about 4-6 per 100,000. The mean duration of the disease is 3 years. About 5,600 people are diagnosed each year in the U.S with the mortality rate approximately the same as the incidence rate, i.e. 2 deaths per 100,000 of the US population annually (ALS Association).

Guidetti et al. (1996) reported that the incidence of ALS in the literature ranges from 0.4 per 100,000 person-years in Mexico City to 2.6 in Varmland County, Sweden. In a population-based study of ALS in western Washington State, incidence for men and women, age-adjusted to the 1990 US population, was reported as 2.1 and 1.9 per 100,000, respectively (McGuire et al.

1996). While some report that the incidence of ALS appears to be increasing over time, others feel that factors such as fewer competing risks, improved life expectancy, and/or improved case ascertainment may explain the trend (McGuire et al. 1996).

Proctor et al. (1992) report a prevalence of ALS of approximately 4 to 6 cases per 100,000 individuals per year in the U.S. population. A review by Roman (1996) of prevalence of ALS worldwide showed a range of 0.8 to 8.5 per 100,000, with US prevalence (from several studies) at 6.4 per 100,000. A recent review by Hirtz (2007) reported the median prevalence from studies as 4 per 100,000 with little variation around the world. Turabelidze (2008a) ascertained cases in Jefferson County, Missouri and estimate period prevalence of 4.2 per 100,000 for 1998-2002.

Prior to 1996, ALS mortality rates varied from 0.5 to 2.1 per 100,000; although more recent studies have suggested greater variation and an increase of ALS cases and deaths (Guidetti et al. 1996). Roman (1996), in his review of worldwide ALS mortality rates, reported wide variations in international mortality rates, probably representing differences in death certificate reliability and methodologies. Average age-adjusted mortality rates ranged from 1.51 (Italy) to 3.81 (Sweden) per 100,000 person years (for ages 40 and over).

ALS is about 20% more common in males than in females (Armon 2001). Age at onset may vary from 40 to 70 years old, although others may develop the disease as well (ALS 2000). The duration of the disease can vary from 2 to 5 years after which most cases die from the disease or other complications. However, some individuals have lived as little as one year and as long as 20 years (ALS 2000).

Although recent advances in ALS research have resulted in the development of some drug therapies, the primary approach to management of the disease is symptomatic treatment. The average life expectancy is 3 years from diagnosis for the majority of patients. The most common form of ALS is called Sporadic ALS. About 5 to 10 percent of cases are the inherited variety known as Familial ALS.

Middleborough was the focus of one study of ALS that arose from community concern about a perceived cluster of the disease (Proctor et al. 1992). In 1987, town officials identified 11 possible cases of ALS in Middleborough (1980 population: 16,404). Proctor et al. investigated further to find a total of 17 ALS cases that had been Middleborough residents at

some time over a 50-year period (1938-1988). Based upon death certificate data, the researchers estimated the ALS death rate in Middleborough for the period 1969-1985 to be 2.5 deaths per 100,000 person years, compared to the statewide rate of 1.26 per 100,000 person years. Although Proctor et al concluded that the increase was not statistically significant (at the 95% confidence level), they also recognized the difficulties in evaluating possible neurological disease clusters.

2.1.4 Etiology and Risk Factors

ALS is characterized in the epidemiological and medical literature as a complex or multifactorial disease. Both genetic and environmental factors are thought to contribute to the pathogenesis of the disease. It is the complex interaction between genetic factors and environmental or exogenous factors that contributes to ALS being a difficult disease to study.

Genetic analysis has shown that mutations in a single gene can initiate a process that leads to selective degeneration of motor neurons (Rowland and Schneider 2001). Observations of familial ALS indicate that there are multiple familial forms (Armon 2001). The most common form of inheritance is autosomal dominant, however recessive genes have been identified as well. Not all carriers of a dominant gene will develop ALS. To date, three genes and linkage to four additional gene loci have been identified as “major” genes (that is, show a clear inheritance pattern) for ALS (Majoor-Krakauer D et al. 2003). In addition, so-called “susceptibility” genes have been proposed that are thought to lead to ALS only in the presence of other genetic or environmental risk factors. Susceptibility genes that are thought to potentially contribute to the development of ALS include neurofilament genes, excitotoxicity genes, and genes involved in protein-protein interactions and mitochondrial metabolism (Majoor-Krakauer D et al. 2003).

Cluster studies of ALS were first initiated in Guam in the 1950s where researchers noticed that the incidence of ALS was much higher than anywhere else in the world. Studies found that the people of Guam cooked with flour made from cycad seeds; these seeds contain a potent neurotoxic chemical that is thought to lead to the development of ALS and also Parkinson’s disease (Roman 1996; Steele and Guzman 1987; Eisen and Hudson 1987). Three other clusters of ALS have been identified on Pacific islands. These include two areas of the Japanese Kii peninsula, the western coast of former West Papua, New Guinea (now Irian Jaya in

Indonesia), and on Groote Eylandt in the Gulf of Carpentaria in North Australia (Majoor-Krakauer D et al. 2003).

In a workshop convened by the ALS Association, leading experts in the field of epidemiology and neurodegenerative diseases concluded that although not conclusive or uniformly reproducible, some human ALS studies have suggested associations between select environmental factors and the disease (ALS 2002). Occupational exposure to neurotoxic heavy metals and solvents has been researched, with inconclusive findings (Kamel et al. 2002; Armon et al. 1991). Several occupational studies have suggested that exposure to lead and certain heavy metals may be associated with an increased risk of ALS and other motor neuron diseases (Guidetti et al. 1996; Mitchell 2000). Other studies have suggested that exposure to agricultural chemicals (Chio et al. 1991; Kalfakis et al. 1991; Gunnarsson et al. 1996; Bharucha et al. 1983; McGuire et al. 1997) and solvents (Hawkes et al. 1989) may be associated with ALS. Other studies, however, have contradicted these findings (Kurtzke 1991; Armon 2001; Gresham et al. 1986). Additionally, studies of geo-chemical elements such as iron, cobalt, nickel and silicon have shown an association with ALS (Roman 1996).

In a review article of ALS, researchers reported additional proposed environmental risk factors for ALS as including a history of trauma to the brain and spinal cord; strenuous physical activity; exposure to radiation, electrical shocks, welding or soldering materials; and employment in paint, petroleum, or dairy industries. They conclude that none of these risk factors have been reported consistently (Majoor-Krakauer D et al. 2003). Finally, a study of Kamel et al. (1999) found an association between cigarette smoking and ALS.

2.2 Multiple Sclerosis

2.2.1 The Disease

Multiple sclerosis (MS) is an autoimmune disease that attacks the central nervous system (National Multiple Sclerosis Society 2001a). Through an inflammatory process, it damages and destroys the myelin sheath that surrounds and protects nerve fibers in the brain and spinal cord (the central nervous system). The damaged myelin may form scar tissue (sclerosis); the scar tissue or lesions in the brain and spinal cord are called “plaques”. MS can also damage the nerve fiber itself. When damage to the myelin sheath or nerve fiber occurs, nerve impulses to and from the brain are distorted or interrupted, causing the brain to atrophy. The symptoms of MS include

tingling, numbness, painful sensations, slurred speech, and blurred or double vision. Some people experience muscle weakness, poor balance, poor coordination, muscle tightness or spasticity, or paralysis (which may be temporary or permanent). Other symptoms include fatigue and bladder, bowel, or sexual function problems. MS can also cause mood swings and cognitive changes such as forgetfulness and difficulty concentrating.

2.2.2 Patterns of MS

Usually, the clinical course consists of a series of remissions and relapses that become progressively more severe over time (Hauser 1994). Although the course of the disease is unpredictable, some general patterns have emerged. These include relapsing-remitting MS (where attacks are followed by periods of partial or total remission), primary-progressive MS (where the disease worsens steadily from the onset), secondary-progressive MS (where the disease worsens progressively after experiencing a relapsing-remitting course), progressive-relapsing (where the course is progressive but there are intermittent exacerbations that partially remit), and inactive MS (where the disease is characterized by fixed neurological deficits of variable magnitude) (Hauser 1994; MDPH 2002). The progress, severity, and symptoms in any one person cannot be predicted.

2.2.3 Epidemiology

Using data collected in the National Health Interview Survey for 1989 through 1994, the overall prevalence of MS is estimated to be 85 cases per 100,000 population. In general, MS is more common in temperate climates than in the tropics, explaining why some studies in the US have shown that MS occurs more frequently in the northern areas of the country than in southern areas (Hernan et al. 1999; Hogancamp 1997; Sorensen 1998). The National Multiple Sclerosis Society estimates the prevalence of MS in the US to range from 57 to 78 cases per 100,000 for states below the 37th parallel to 110 to 140 cases per 100,000 for those above the 37th parallel (National Multiple Sclerosis Society 2002b). In a review of community-based prevalence studies of MS in the United States, Noonan et al. (2002) reported prevalence estimates in the literature ranging from 39 to 173 cases per 100,000 people. As representative of the period prevalence of MS in a southern latitude area, a 19 county Texas study estimated prevalence at 42.8 per 100,000 (Williamson, 2007). A recent review article by Hirtz (2007) reported the median prevalence from studies in northern North America as 200 per 100,000 (ranging from

170 to 230 per 100,000). Two studies in Missouri, one by Neuberger (2004) and one by Turabelidze (2008b), found period prevalence estimates of 113 and 105 per 100,000, respectively. Based on the National Multiple Sclerosis Society estimates, some 6,930 to 8,820 individuals in Massachusetts have multiple sclerosis (MDPH 2002).

As with prevalence estimates, some variability exists in reported incidence of MS. Using data from the Nurses' Health Studies, Hernan et al. estimated age-specific incidence of MS ranging from 18.9 per 100,000 women-years for 40-44 year old women to 3.4 per 100,000 women-years for 65+ years of age. Using incidence from 16 published studies, Jacobson et al. (1997) estimated a weighted mean incidence of MS to be 3.2 cases per 100,000 people in 1996 in the US. In his review of the epidemiology of MS, Weinshenker (1996) reported an estimated annual incidence for MS, based on data from Olmsted County, Minnesota, of 7 to 8 new cases per 100,000.

Two literature reviews reported that some evidence exists that the prevalence and incidence of MS appear to be increasing over time. Weinshenker (1996) states that there is evidence that the incidence of MS is increasing in some areas but that it is difficult to know if this is due to improved diagnoses procedures and ascertainment. Jacobson et al. (1997) reported that prevalence values for MS show an increasing trend with time when examining the 30-year period between 1965 and 1995. They cautioned that causes for the increase have not been ruled out, such as better diagnosis, improved study design, or higher-risk populations being studied.

Multiple sclerosis occurs more frequently in women than men and in whites than non-whites. Noonan et al. (2002) reported that the ratio of MS in women to men is 2.6 to 1. MS is also more common among Caucasians than in other races with the incidence of MS in white Americans approximately twice that in African-Americans (Hogancamp et al. 1997). Caucasians of northern and central European ancestry, particularly people of Scandinavian descent, are at highest risk of developing MS, although people of all races and ethnicities may be affected (ATSDR 1999). MS is most frequently diagnosed in adults between the ages of 20 and 40, with prevalence highest in the 40 – 59 year age range (Noonan et al. 2002).

Migration studies support the role of environmental factors in disease acquisition and/or disease onset. These studies indicate that migrants from one area can acquire the MS disease risk of their destination area, but this relationship appears to be sensitive to the age at migration.

For example, studies of immigrants and their children in Israel, Great Britain, and California have found that persons who immigrate after puberty bring with them the MS risk of their country of origin, whereas those who immigrate before puberty take on the risk of their adopted country (Alter 1966). Recent studies from Australia, however, have indicated that the timing of migration and the associated risk of MS may be more complex than previously described (Hammond 2000).

2.2.4 Etiology and Risk Factors

Although the cause of MS is unknown, epidemiological studies support both genetic and environmental components of susceptibility (Hogancamp 1997; Compston and Coles 2002; Willer and Ebers 2000). Both Compston and Coles (2002) and Willer and Ebers (2000) concur that MS is a disease resulting from the complex interplay of genes and environmental factors. The National MS Society characterizes MS as a disease that is not directly inherited but one for which those afflicted carry a genetic predisposition for the disease (National Multiple Sclerosis Society 2001b). Evidence suggests that MS is a multigenic disease; that is, there may be many separately inherited genes that contribute to susceptibility to MS. No single gene has been found to be responsible for the disease. In addition, the National MS Society believes that MS may be triggered by something in the environment, such as an infectious viral or bacterial agent. It may be that no single agent will ever be shown to exert a cause-and-effect relationship but rather that people with genetically predisposed immune systems may react to certain bacteria or viruses or other environmental agents in a way that results in the expression of MS.

As mentioned earlier, multiple sclerosis is not thought to be hereditary, but having a first-degree relative (i.e., parent or sibling) with MS increases an individual's risk of developing MS (Hauser 1994; Sorensen 1998). In a large, long-term study involving 370 Canadian twin pairs, researchers tracked disease concordance (meaning that both twins have the disease) between identical twins, non-identical twins, and non-twin siblings. They reported recently that the overall risk of MS for identical twins was 25% (1 in 4), for non-identical twins was 5.4% (1 in 20), and for non-twin siblings was 2.8% (3 in 100) compared to the general risk of MS in a person who does not have a sibling or parent with MS of 0.1% (or 1 in 1,000) (National Multiple Sclerosis Society 2003).

Although there is little evidence for a single or unique environmental cause of MS (Hogancamp et al. 1997), some research studies have reported associations between MS and certain occupations, environmental exposures, or other putative risk factors. These studies number in the hundreds, with factors including exposure to organic solvents, metals, low temperatures, trauma, diet, socioeconomic status, and allergies. In a review article on the role of viruses in the pathogenesis of MS, the authors conclude that multiple viral agents may induce an autoimmune response resulting in clinical MS, even though no single viral agent has been firmly associated with MS (Soldan and Jacobson 2001). The consensus appears to be that both susceptibility genes and various environmental factors may play a role in the development and expression of MS.

3.0 Methods

3.1 Surveillance Population

Figure 1 is a map of the surveillance area, which is comprised of 30 communities in Southeastern Massachusetts. Middleborough (and Raynham) and communities that surround the South Weymouth Naval Air Station (SWNAS) (Abington, Rockland, and Weymouth) are towns within the surveillance area where ALS and MS have been identified as community concerns. In the communities surrounding the SWNAS, community concern exists about possible associations between the occurrence of these diseases and historical exposures to metals and chemicals used at the Base during its six decades of operation. Several hazardous waste sites are located in Middleborough and adjacent communities and the role of these sites in relation to disease occurrence was also of concern to local residents. Table 1 provides a breakdown of general characteristics for the surveillance population, including gender, age, and race (based on US Census Bureau 2000 data). The total population for the surveillance area is approximately 546,000, with 90% white, 4% black, 2% Hispanic or Latino, 1% Asian, and less than 1% other races.

3.2 Case Definition

An individual was eligible for inclusion in the study if (a) the medical record included a statement that the patient had a diagnosis of ALS or MS before or during the surveillance period of January 1, 1998 to December 31, 2003, (b) who had a documented physician visit during this six-year period, and (c) who reported their residence during an office visit during the surveillance period as being in the surveillance area.

Diagnostic criteria for ALS, developed by the World Federation of Neurology Research Group on Neuromuscular Diseases at El Escorial, are proposed for use in surveillance (Brook 1994). Using these criteria (referred to as the El Escorial criteria), the diagnosis of ALS requires the presence of the following:

- signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathological examination,
- signs of upper motor neuron (UMN) degeneration by clinical examination, and
- progressive spread of signs within a region or to other regions together with the absence of electrophysiological evidence of other disease processes that might

explain the signs of LMN and/or UMN degeneration and neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysical signs.

A diagnosis of ALS can be made based on clinical evidence alone, and specific criteria exist for such a diagnosis, or it can incorporate the use of electrophysiological, neuroimaging, clinical laboratory, and/or neuropathological features, each having specific criteria and guidelines as well. For this investigation, we defined a verified ALS case as one classified as either as definite or probable ALS based on the El Escorial criteria allow for categorization of ALS.

For MS, both the Poser diagnostic criteria (Poser et al. 1983) and revised diagnostic criteria (McDonald et al. 2001) developed by the International Panel on the Diagnosis of MS were used for surveillance. The Poser criteria categorize patients as clinically definite MS, laboratory-supported definite MS, clinically probable MS, or laboratory supported probable MS. These categories lend themselves to the identification of a case as either definite or probable. The newer McDonald diagnostic criteria were designed to reflect improved understanding of the disease and new technologies, to integrate magnetic resonance imaging (MRI) into the overall diagnostic scheme, to simplify the diagnostic classifications, and to retain the most useful features of the Poser criteria. Using the 2001 criteria, an individual is usually classified as either having MS or as not having MS, or if the evaluation meets some but not all of the necessary criteria, as having possible MS. Tables 2 and 3 present a summary of the Poser and McDonald diagnostic criteria, respectively. Cases categorized as definite or probable MS according to the Poser criteria AND definite MS according to the McDonald criteria were considered verified MS cases.

3.3 Data Sources

Because no single data source is likely to identify all cases, we relied on several different case-finding methods to ascertain cases. The relative merits of different methods vary for MS and ALS because the clinical course of the two diseases is very different. For example, death certificates would be expected to be a low-yield case-finding method for identifying MS cases, given that the disease course for MS is often prolonged, sometimes for decades. For ALS, because of the rapid progression of the disease, with most cases dying within two to five years of diagnosis, this case-finding method would be expected to be a more efficient way to identify

ALS cases in a given community than MS cases. However, surveillance systems designed to identify individuals while still alive provide optimum chances for learning more about risk factors and disease progression. For this investigation, we classified data as coming from one of two sources: primary and secondary.

3.3.1 Primary Data Sources

Two primary sources were available for case identification: private neurology practices and MS/ALS inpatient and outpatient records in hospitals. The majority of the cases were thought to be best identified through these sources. This expectation was supported in the epidemiological literature (Nelson and Anderson 1995). Nelson and Anderson conclude that, more than any time in the past, people with neurological symptoms and/or disease are much more likely to seek the care of a neurologist or be referred to a neurologist by their primary care physician. In a prevalence survey of MS in northern Colorado, a review of neurology practice records was the leading case-finding method, yielding 71% of all the prevalent cases and serving as the sole source of identification for 32% of all the cases (Nelson and Anderson 1995).

The neurology professionals that serve the residents of the surveillance area were identified through discussions with consulting neurologists and representatives of several patient advocacy groups for ALS and MS. In addition, neurologists in the surveillance area communities were also identified using the following resources:

- The Massachusetts Board of Registration in Medicine's website (www.massmedboard.org),
- Directory of the Massachusetts Neurological Society,
- The Official ABMS [American Board of Medical Specialties] Directory of Board Certified Medical Specialists 2002, and the
- Folio Medical Directory Massachusetts.

Because of the proximity of the surveillance area to Boston, many patients are diagnosed in MS and ALS clinics in Boston hospitals. Approximately 15 hospital clinics in Boston and 55 private neurologists in the surveillance area were identified as providers of care to ALS and MS patients living in Southeastern Massachusetts. In addition, requests for patients were submitted to Brown University Hospital's ALS clinic in Providence, Rhode Island and to the U.S. Navy for patients who may have served at the SWNAS.

Private neurology practices in Boston proper were not contacted. Although it is possible that a surveillance area resident with MS or ALS may seek ongoing treatment at such a practice, it was thought that the record search at hospitals and clinics and the review of cases from secondary sources would allow us to capture these cases. He or she would be much more likely to seek a diagnosis and/or treatment at the well known MS and ALS clinics in Boston hospitals and our record search included Boston clinics.

3.3.2 Secondary Data Sources

Secondary sources of data included Massachusetts' death certificates, information from the MDPH Multiple Sclerosis Program (a former MDPH program to help provide palliative care services to referred patients), and databases maintained by patient advocacy groups. These records were attempted to be used to determine if any cases might possibly have been missed relying on primary data sources only. In addition, requests for cases from HMOs in Plymouth County (which constitutes most of the study area) were also made.

The MDPH held several meetings with patient advocacy groups to discuss accessing their patient databases; these groups include the ALS Family Charitable Foundation; the ALS Association, Massachusetts Chapter; and the MS Society, New England Chapter. Historically, the Muscular Dystrophy Association (MDA) has also provided support to some ALS patients in Massachusetts but a decision regarding access to their database could not be obtained from either the local or National MDA. Because of the nature of the illnesses, most patients contact these patient advocacy service organizations for some type of assistance and to stay abreast of research and clinical findings.

3.4 Case Ascertainment

Case ascertainment from both primary and secondary sources had the initial goal of determining if an identified case met the case eligibility criteria (refer to section 3.2). Case ascertainment from primary sources began in August 2004 and was completed in August 2005. Case ascertainment from secondary sources also began in 2004 but was ongoing through 2005 to accommodate the time necessary to arrange for informed consent or to prepare datasets. Mortality files for the period ending December 31, 2003 were not available until late 2005.

MDPH contacted neurologists and hospitals in the area requesting their participation in the surveillance project and describing what participation means in terms of case identification,

record retrieval and patient confidentiality (*see* Appendix 1). MDPH followed up the letter of introduction with a call to schedule an office visit and request that a list of possible cases be prepared using either billing records or an internal office database. ICD codes were provided to facilitate this process.

ICD-9-CM codes have been used for standard disease coding purposes beginning in 1979 and was used by hospitals and health professionals throughout the data collection period (ICD – has now been replaced by ICD-10). Any records with the ICD-9-CM codes listed in Table 4 were requested for review. With respect to ALS, in addition to the ICD code for ALS, codes were included for progressive muscular atrophy and bulbar palsy. These diseases are clinical variants of ALS that usually progress to ALS. Progressive muscular atrophy involves the lower motor neurons but typically progresses to the upper motor neurons. Similarly, progressive bulbar palsy involves the upper motor neurons but usually progresses to the lower motor neurons.

In addition to the ICD code for MS, additional codes representing conditions related to MS were included. For example, transverse myelitis, coded as 323.9, carries a high risk of MS. In addition, optic neuritis is a frequent feature of MS. For 14 to 18% of MS cases, optic neuritis is the initial monoregional attack of MS, and for 22 to 41% it is part of the first polyregional attack (Coyle 2000). By including these codes, it was hoped to identify cases that may otherwise have been missed because of coding issues and differences.

Because some medical records did not include ICD codes, office personnel were asked to pull the medical records of individuals who are thought to have MS or ALS in order for project staff to review the records and determine if they included a statement of diagnosis by the physician.

Four nurses with professional experience in neurology were trained to identify a statement of diagnosis by a physician and to abstract the required clinical information from the records. Training was conducted by consulting neurologists and their neurology nursing staff. A copy of the medical record abstracting short form used when visiting neurologists' offices is included in Appendix 2. The abstractor used the short form to determine if a patient met the case definition. Appendix 3 contains the abstracting long forms with separate forms for ALS and MS patients. The long forms were used to abstract the required clinical information from the medical

records, including the physician's impression of the diagnosis. The physician's impression was the basis for determining if there was a clear statement of diagnosis in the medical record. Abstraction was done using a passphrase-protected laptop. The electronic version of the abstraction forms were prepared in ACCESS and incorporated drop-down boxes for categorical responses and text boxes for more detailed and varied responses. The nurses downloaded abstracted information weekly at the MDPH office so that it would remain on the laptops for as short a period of time as possible.

Case ascertainment methods from secondary sources was variable depending upon the type of secondary source. For all types of secondary sources, an identified case was initially reviewed to determine if it met the case eligibility criterion of residence within the study area during the surveillance period, since medical records were not available at the time of case reporting to establish diagnosis. Appendix 4 contains a template letter that was provided to the MS/ALS advocacy groups to notify their clients of the surveillance project and request their consent to share their name with MDPH. The intent was to request the medical record of the patient to confirm their diagnosis and determine if the patient met the definition of a case after the advocacy group obtained patient consent. However, because the records of interest were often for individuals who were no longer active cases, the necessary information to locate and review the medical record was often not readily available. Therefore, efforts were limited to determining if the case had already been reported and if the individual met the residential definition of an eligible case. Appendix 5 contains a tracking form used for logging self-referrals.

Massachusetts' death certificate data were accessed to identify individuals in the study area who died during the surveillance period, and whose death certificate included any ICD code for MS or ALS. The Registry of Vital Records and Statistics within the MDPH collects and records Massachusetts' death certificate records. Records are computerized according to city/town of residence from 1969 to the present. Deaths were requested for the period January 1, 1998 through December 31, 2003. Since 1999, the Massachusetts Registry of Vital Records and Statistics has used ICD-10 codes on death certificates to document cause of death or the presence of disease. Prior to that, ICD-9 codes were used. Individuals with the specific ICD codes for MS or ALS on their death certificate and with a residence reported on the death certificate in one

of the 30 surveillance area communities were considered for inclusion in a secondary case file, which was linked and cross-checked with the primary case file (ICD codes are listed in Table 4). The following information was downloaded on each decedent: name, gender, date of death, place of death, underlying cause of death, other mentioned conditions, race/ethnicity, date of birth, street address, and town of residence on the death certificate. The eligibility of cases identified through death certificates could not be established because date of physician visits is not included on death certificates and because a diagnosis of ALS or MS cannot be assumed without verification. This is especially true with regard to death certificates coded using the newest set disease classification codes, ICD-10. This is because there no longer is a specific code for ALS in ICD-10 but only a set of codes for the broader category of motor neuron disease MS still has a specific code under ICD-10). Therefore, these could only be considered as potential ALS or MS until verification of the diagnosis. These cases were used in the assessment of completeness of case ascertainment.

Data maintained by the MDPH Division for Special Health Needs through its Multiple Sclerosis Program also were reviewed. Specifically, the identification of individuals with MS who had contacted the Division for assistance was sought. The years included calendar year 2000 (the first year of the MS Program) to the present. The following variables from the MS Service Coordination Intake Form database were obtained: name, date of birth, address, gender, race/ethnicity, and date of diagnosis. As with cases identified through death certificates, case eligibility could not be established but these potential cases were considered in the assessment of completeness of case ascertainment.

3.5 Verification

One of the project's objectives was to evaluate the surveillance methodology used to estimate the prevalence of MS and ALS. This consisted of evaluating the completeness of case ascertainment and the verification of diagnoses reported in medical records from primary sources. Cases reported from secondary sources were not verified because of resource limitations

For ALS, because of the small number of expected cases, 100% of the cases identified from primary sources were reviewed by a consulting neurologist in order to verify the diagnosis according to the standardized diagnostic criteria. For MS, case verification was conducted on

approximately 10% of the total number of records abstracted. Block randomization was used to select an MS patient's record for full abstraction and verification. The abstracted MS records were ordered (after completion of the medical record short form) to facilitate sampling. For every 10 records, a number between one and 10 was chosen from a table of published random numbers to identify one of the 10 records for which the abstraction long form would be completed. The consulting neurologist reviewed this abstracted information independently, to confirm the abstractor's characterization of a patient as having a diagnosis of ALS or MS. If fewer than 10 cases were identified in a practice or clinic, then at least one medical record was selected to be fully abstracted for verification. In addition, if an abstractor was unsure whether to characterize a case as a clear diagnosis of ALS or MS, based on the stated physician's impression within the medical record, a long form for that case was also completed to allow for review by the consulting neurologist.

3.6 Geocoding Case Information

GIS technology (geocoding), spatial analysis and investigation, thematic mapping and reporting were also used. To ensure spatial accuracy of geocoded data, MDPH used high-quality street reference data known as GDT Dynamap/2000. Dynamap data are more spatially accurate and their attribute information more complete than any free dataset currently available such as Census Tiger/Line files.

The street address for each case was obtained and geocoded. If a street address was not included with the medical record or the address was determined to be invalid, annual town census data and other public address sources were researched to obtain the correct street address.

3.7 Data Management

A relational database containing case and source information was created using Microsoft Access and SAS software. Data fields were created to record information collected on the medical record abstracting forms. The system was designed to allow for the identification of duplicate cases (that is, cases identified by multiple sources).

Prior to data analysis, information entered into the electronic database was assessed for the purpose of quality assurance to check for data collection errors, data entry errors, and inconsistencies that might require re-entry or re-abstraction of a medical record. Figure 3 presents a flow chart summarizing data collection milestones in the case ascertainment process.

At the completion of a “clean” database, the primary and secondary case files were linked to identify duplicates. A final analytic case file consisted of only those individuals that met the definition of a case. All electronic data files were password protected and paper files were kept in locked file cabinets accessible only to project staff.

3.8 Data Analysis

Prevalence estimates were obtained and evaluated for the study area. Crude prevalence estimates of MS and ALS were calculated for the surveillance area where prevalence was defined as the number of affected individuals in the population at a specific time (point prevalence) or over a specific period of time (period prevalence) divided by the number of persons in the population at that time. In this study, point prevalence was estimated on December 31, 2003 and period prevalence was estimated for the 1998-2003 period for ALS and MS. In addition, period prevalence was used for the 1998-2001 period estimates when comparisons of MS prevalence were made to the reference population (in order that the period prevalence definitions were the same). Prevalence estimates were not age-adjusted.

Point Prevalence per 100,000 =

$$\frac{\text{\# of cases alive in the surveillance population on December 31, 2003}}{\text{\# of persons in the surveillance population on December 31, 2003}} \times 100,000$$

Period Prevalence per 100,000 =

$$\frac{\text{\# of cases present in the surveillance population during the surveillance period}}{\text{\# of persons in the surveillance population during the surveillance period}} \times 100,000$$

The numerator was estimated using the final analytic case file. The denominator was estimated using Census 2000 data for the surveillance cities and towns, as closely representative of the mid-year of the study period. Ninety-five percent confidence intervals were calculated for each prevalence estimate. The formula (Chap and Boen 1995) for 95% confidence intervals (CI) for prevalence follows:

$$P \pm 1.96\sqrt{P(1-P)/N}$$

Where P is prevalence and N is the total surveillance population. When the number of observed cases for ALS or MS was less than 600, 95% confidence intervals were calculated based upon the Poisson distribution (Daly 1992).

Point prevalence estimates for ALS were used for statistical comparisons with a representative estimate for areas outside of Massachusetts to determine if prevalence in the study area appears unusual or higher than observed elsewhere. Point estimates were used because no comparison numbers are known for period estimates using the same comprehensive data collection methods as those used in this study. The scientific literature generally reports point prevalence estimates for ALS.

For ALS, three studies were identified that reported crude point prevalence estimates (per 100,000) after ascertaining cases from medical records:

Traynor 1999	Ireland	4.7 (95% CI 4.0-5.5)
Mandrioli 2003	Modena, Italy	4.0 (no CI)
Turabelidze 2008a	Jefferson County, Missouri	3.9 (95% CI 1.7-7.7)

Even though the prevalence estimate in the Missouri study was based on a small number of cases, it was selected as the reference prevalence value in statistical analyses because the methods of case ascertainment most closely matched those in this study.

When the prevalence of MS within the study area was compared to estimates outside of Massachusetts, period prevalence was used. Studies reported in the scientific literature applying the data collection methods used in this study generally report period prevalence.

For MS, three U.S. studies were found that generated crude period prevalence estimates (per 100,000):

Neuberger 2004	Sugar Creek/Independence, Missouri	115 (95% CI 94-139)
Turabelidze 2008b	Jefferson County, Missouri	105 (95% CI 91-121)
Williamson 2007	19 County Texas study	42.8 (95% CI 37-50)

The Missouri studies are closest to the latitude of Massachusetts and were the most appropriate to use for comparison. The higher of the two Missouri estimates was selected as a conservative reference measure (115 per 100,000) for the statistical analyses, where the prevalence period was 4 years (1998-2001).

As a measure of effect of the prevalence of MS and ALS in different geographic areas (for example, surveillance area-wide prevalence to SWNAS area-specific prevalence or to the Missouri estimates), prevalence ratios were calculated as follows:

$$\text{Prevalence Ratio} = (P_1) / (P_0)\#$$

Where P_1 is the prevalence in the study area and P_0 is the prevalence in the reference area. A ratio greater than 1.0 suggests that the probability of having ALS or MS is higher in the study area than the reference area (Pearce 2004). Only prevalence estimates based on verified diagnoses were used to compare with the reference area since those are what the reference estimates are based on.

When differences in prevalence were assessed to determine if they were statistically significant, 95% confidence intervals for prevalence ratios were calculated. Confidence intervals excluding 1.00 were considered statistically significant.

To evaluate the completeness of case ascertainment, as described in the “Case Ascertainment” methods section, various secondary sources were used to assess whether cases would be missed if only primary data sources were used to estimate prevalence. After matching personal identifying information from all sources to identify potential unique cases, the proportion of cases from each source was presented and potential limitations of study methods discussed. When possible missed cases were ascertained, the potential impacts on the prevalence estimates were determined and discussed. This approach included calculating a range of prevalence from assuming no verified diagnoses were missed to assuming all missed cases were verified diagnoses.

3.9 Environmental Analysis

The address location at time of diagnosis of all individuals diagnosed with either MS or ALS was mapped using GIS software. This enabled the geographic distribution of cases to be assessed with respect to their proximity to sources of environmental contamination, such as hazardous waste sites and other industrial sources of pollution, and statistical clustering.

As mentioned, several state/federally designated hazardous waste sites within Southeastern Massachusetts were the focus of the environmental evaluation. These included three MGL c.21e hazardous waste sites in the town of Middleborough and the South Weymouth Naval Air Station (SWNAS) a Department of Defense site on the U.S. Environmental Protection

Agency's National Priority List (NPL). The SWNAS is located in the town of Weymouth, but also abuts the communities of Rockland and Abington, as well as the town of Hingham.

Middleborough Sites:

Historically, Middleborough residents have expressed concerns about the possible association between the occurrence of ALS among residents and opportunities for exposure to contaminants at hazardous waste sites in that community. Concerns have focused primarily on three sites: the Rockland Industries site, a former chemical manufacturing and packaging facility; the Middleborough Plating Company, a former metal plating facility; and the Gerson Company property (a sewage disposal company) where releases occurred from an industrial wastewater and sewage disposal system.

The Rockland Industries site contained several companies beginning in the mid-1960s, including a chemical manufacturing company. Middleborough Plating began electroplating operations in the mid-1960s and continued until 1991, when the property was bought and industrial operations on the property ceased. Although the Gerson Company property was used for sewage disposal beginning in the early 1900s, it was not until the mid-1960s when it was reported that industrial waste from Middleborough Plating was also discharged into the sewage disposal system, making the waste more hazardous. Prior to that, it was assumed that the Gerson facility was used solely for the disposal of sewage.

Historical groundwater, surface water, soil, and sediment contamination has been documented at these sites. In addition, although it is reasonable to assume that air emissions from operations at Middleborough Plating could have resulted in exposure to nearby and downwind residents, it is difficult to estimate to what degree the local population could have been exposed to stack or fugitive air emissions from the site due to the lack of historical emissions data.

South Weymouth Naval Air Station (SWNAS):

The SWNAS is located in the towns of Weymouth, Abington, and Rockland, and in part the town of Hingham. The SWNAS began operating in 1941 and was closed in 1997. Past operations included aviation training, aircraft support, and dirigible operations (i.e., balloon airship). At full capacity, staff numbered 3,750 with 775 people living on the station. The base comprises an area of about 1,400 acres.

SWNAS was placed on the U.S. Environmental Protection Agency's (EPA) National Priority List (NPL) in 1994. The U.S Navy, along with the EPA and MDEP, has conducted numerous environmental investigations at the base in anticipation of transferring the property for public and commercial use. Ongoing environmental investigations, along with continuing community concerns about possible exposures to SWNAS contaminants and suspected increases in the prevalence of MS has led to the inclusion of this site in MDPH's evaluation of ALS and MS.

MDPH used ESRI ArcView geographic information system (GIS) software to perform a spatial analysis of the MS and ALS prevalence data linked with the environmental contamination sources at the state and federal hazardous waste sites described previously. To evaluate potential clustering of ALS and MS cases, the distribution of cases was determined.

To determine the existence of clustering the evaluation was approached in two ways. All methods utilized must control for the population distribution since it would be expected that areas that are more populated would have a greater number of cases. To control for differences in the population and other factors, such as gender, and to protect individual identity, areas defined by census tracts (CT) were obtained to provide disease rates per 100,000 in each CT, when statistically possible.

The first statistical approach utilized two cluster detection methods: the spatial scan statistic and the cumulative geographic residuals test to investigate the existence of any significant clustering in the study area. If significant clustering exists, this would suggest that further evaluation, in relation to the environmental sites, should be considered. The second approach explored the relationship of distance of cases from environmental sites by creating two potential areas to test for spatial clustering; census tracts within 2 kilometers of the sites and census tracts within 5 kilometers. This analysis used the information on the location of the site, but did not take into account the natural variability of disease prevalence in the rest of the area. If both the cluster detection tests and the approach to assess the relationship between distance of cases suggest a relationship between the environmental site and an increased disease rate, it would indicate a need to explore what potential factors or exposure opportunities might play a role.

The spatial scan statistic (SATScan v6.0) forms circles of a range of radii throughout the entire study area. It then calculates a likelihood ratio statistic comparing the rate of a given disease within a given circle versus outside the circle. It does this for all circles and then finds the cluster area where the rate is highest within the circle compared to outside the circle (maximizes the rate ratio). Then it runs a test to see how often this maximum rate ratio could occur by chance and calculates the p-value.

The second statistical clustering method, the cumulative geographic residuals test (CumGeoRes), considers the observed rate of disease minus the expected rate of disease and adjusts for factors like gender. Using this method, a cluster is defined as finding a statistically significantly higher than expected number of observed cases in an area.

3.10 Community Involvement

An integral component of this surveillance was the involvement and support of the medical community and patient advocacy groups. The support and information obtained from these groups contributed significantly to the project's ability to meet its goals. In turn, the MDPH is committed to sharing the surveillance findings with the medical community, advocacy groups, and the public, to enhance awareness of the public health significance of the occurrence of ALS and MS.

The MDPH had the support of several patient advocacy groups: the ALS Family Charitable Foundation, the Massachusetts Chapter of the ALS Association, the Muscular Dystrophy Association, and the New England Chapter of the MS Society. An MS/ALS advisory group was formed during the protocol development stage and held periodic meetings to discuss project status and seek input. This group included representatives from the medical community, advocacy groups, the MDEP, selected local health agents and a community group, AWARES. Through the MS/ALS Advisory Group, we were better able to design a scientifically sound study that met realistic community expectations and develop strategies for the effective dissemination of information.

3.11 Confidentiality

The following state laws and regulations govern the collection of health information for public health surveillance by the Massachusetts Department of Public Health:

- Massachusetts General Laws Chapter 111, Section 24A – Access to MDPH Confidential Data, and
- 105 Code of Massachusetts Regulations (CMR) 300.000 – Reportable Diseases, Surveillance, and Isolation and Quarantine Requirements.

In accordance with MGL c.111, §24A all information collected for public health investigations approved by the Commissioner of Public Health is strictly confidential and is not admissible as evidence in any legal proceeding. The statute also states that anyone providing information to a researcher approved by the Commissioner of Public Health shall not be liable for any damages related to that disclosure.

The MDPH regulatory authority to access health records for the purpose of conducting public health surveillance is granted through regulations cited in 105 CMR 300.192. Under these regulations, the MDPH is authorized to collect from health care providers data (including medical record information) on individuals evaluated for or diagnosed with ALS or MS. The MDPH Human Research Review Committee (HRRC) reviewed the project under the MDPH surveillance regulations and concluded that it does not constitute research involving human subjects and, thereby waived full Institutional Review Board review.

The state regulatory authority also allows covered entities under the Health Insurance Portability and Accountability Act (HIPAA) to disclose protected health information to the MDPH without obtaining written authorization of the data subject. A public health authority is authorized by law to receive such information (see 45 CFR 164.512(b)).

It is the policy of the MDPH to ensure that all public health investigations and studies be conducted in a manner that protects the rights and privacy of human subjects to the greatest extent feasible and that they comply with all applicable state and federal requirements.

As previously discussed, database security included password protected files and encryption. All confidential hardcopy information was kept in locked file cabinets. Confidential information, such as name and address, cannot and will not be shared with the ATSDR, advocacy groups, medical professionals, and/or others beyond the MDPH.

4.0 Results

4.1 Case Ascertainment of ALS

Figure 2a presents the flow in number of cases from initial case ascertainment through diagnostic verification and prevalence estimation. The surveillance of ALS in Southeastern Massachusetts identified 43 cases with a clear statement of diagnosis based upon the physician's impression, as recorded in the medical record, during the course of the full surveillance period. Because some had died during the study, the number of cases alive on December 31, 2003 was 30.

Of the 43 cases, about 91% were identified from a single data source and all but 3 of those were identified from hospital inpatient records (Table 5). Only 4 cases were found in both hospital records and private practice neurologist' records.

Table 6 shows that the number of reported cases was slightly higher among females than males (53.5% and 46.5%, respectively). Individuals aged 70 and greater had the highest percentage of cases (41.9%). The number of cases was also higher in the 50-59 and 60-69 age groups (25.6% and 16.3%, respectively). Race and ethnicity information in medical records was found to be missing or unreliable for most cases (79.1%).

Table 7 shows the number of cases identified from sources other than medical records (i.e., secondary sources). These include death certificates, patient advocacy groups, community advocacy groups, and federal hospitals. As discussed, the intent was to compare the names of reported cases from these sources with those obtained through the primary data sources in order to evaluate the accuracy of the prevalence estimated from the primary data sources. Medical records could not be reviewed to confirm whether the patient met the study case definition, as was done for the cases from the primary sources.

As shown in Figure 2a and Table 5, the total number of secondary source cases not reported by a primary source (excluding cases from death certificates) was 7. There were 6 cases identified from ALS patient advocacy groups. Although, the medical records of these cases were not reviewed, each of the 6 cases completed a consent form that indicated that the eligibility criteria of diagnosis, date of physician visits and residence were met. There was 1 case identified from a federal hospital. Two data sources listed in Table 5, the West Roxbury Veterans Administration Hospital (VA) and the Rhode Island Naval Hospital, are primary sources in that

they are hospital neurology practices, but were treated as secondary sources because there were no medical records available. Names of VA cases were provided but for federal privacy reasons, necessary information such as diagnosis, age, and residence were not available and medical records were not permitted to be reviewed. As a result, it is unknown how many or if any ALS cases diagnosed and treated at the VA were eligible cases and no cases were considered reported from this source. The U.S. Navy provided cases for employees and their dependents that may have worked or lived at the SWNAS and been treated at the Rhode Island Naval hospital. Two cases were identified, though one had been previously been reported by a primary source. Of these 7 secondary source cases, 4 were alive on December 31, 2003.

The largest group of secondary cases was identified from death certificates. There were 58 ALS deaths during the surveillance period and 45 were cases not found through primary data sources. Death certificates were reviewed to determine if ALS was stated as a cause of death. However, information contained on the death certificates was insufficient to determine if case eligibility might have been met.

4.2 Prevalence of ALS

Period prevalence is used to present the burden of disease for the full study period. The period prevalence for the full surveillance period prior to the verification of diagnosis and excluding cases from secondary sources was estimated at 7.9 per 100,000 per time period. Appendix 6 presents the period prevalence and 95% confidence intervals for each study community based on the diagnoses reported in the medical records. Because ALS is a rare disease, many communities had no cases during the period 1998-2003. Those that did have a case of ALS never had more than 5 cases. Duxbury had the highest prevalence (35.1 per 100,000 95% CI 11.4-81.8). Due to the small number of cases in any individual community, the confidence intervals were very wide, indicating that the prevalence estimates were imprecise.

As discussed in the methods section, an important component of disease surveillance and an important objective of this project was the verification of diagnoses using standardized diagnostic criteria. In addition, point prevalence was estimated based upon the verified diagnoses in order to make comparisons with prevalence estimates found in the scientific literature, which generally were available only as point prevalence.

Table 8 presents the results of the verification of diagnoses. All medical records from primary sources were reviewed by a neurologist. Standardized diagnostic criteria, El Escorial, were applied and 44.2% of the records reviewed were confirmed as definite or probable ALS. Most of the diagnoses not confirmed were determined to represent possible ALS, although the records of 9 cases could not be reviewed due to incomplete clinical information necessary to apply the diagnostic criteria (verification percentage of cases with complete medical records = 55.8%).

Tables 9a present estimates of point prevalence estimate for the total study area for verified cases of definite or probable ALS. Prior to the verification of diagnosis, there were 30 ALS cases identified that were alive on December 31, 2003. This represents a point prevalence estimate of 5.5 per 100,000. As Table 9a shows, when only verified cases are considered, the point prevalence estimates is 2.4 per 100,000 (95% CI 1.3-4.0). This estimate was lower than the prevalence in the reference area (3.9 per 100,000; 95% CI 2.0-7.7). Crude prevalence ratios were calculated to compare the study and reference areas. The prevalence ratio was 0.61 with a 95% CI of 0.25-1.46, indicating that the two estimates were not statistically significantly different.

Table 9b presents a chart showing how point prevalence might vary if some cases that were reported as ALS but that could not be verified are definite or probable ALS because necessary medical records could not be reviewed. Case category 1 presents the minimum prevalence of ALS in the study population (2.4 per 100,000; 95% CI 1.3-4.0) and is the most reliable estimate from this study because it is based upon verified diagnoses only. Case category 2 additionally includes some cases reported from patient advocacy groups and from primary sources whose records were incomplete and, consequently, diagnoses could not be verified (the RI Naval Hospital case was included). If the verification percentage of primary source cases (44.2% - refer to Table 8) is applied to these cases, then 2 additional “verified” cases from secondary sources and 2 “verified” cases from the primary source cases that were not able to be reviewed could be assumed to be definite or probable ALS for a total of 17 cases. The point prevalence estimate would increase to 3.1 per 100,000 (95% CI 1.9-4.9). Case category 3 represents the maximum prevalence possible and assumes all advocacy cases and all non-reviewed primary source cases are definite or probable ALS (4.0 per 100,000; 95% CI 2.6-6.0).

Because of the small number of ALS cases in individual towns, the prevalence of ALS near the SWNAS and the Middleborough sites could not be reliably compared with the reference or total study area. The number of ALS cases in Weymouth, Abington, and Rockland combined was 10. The distribution of ALS cases did not appear unusual or geographically grouped together within these communities. No cases were identified in Middleborough during the study period.

4.3 Case Ascertainment of MS

Figure 2b shows the sources and numbers of MS cases ascertained for the prevalence estimates and comparisons of prevalence conducted in this study. From the 70 hospitals and neurology practices contacted, there were 800 cases identified meeting the case definition for the full surveillance period (1998-2003). Each had a clear statement of diagnosis of MS based upon the physician's impression recorded in the medical records. As shown in Table 10, 75% of the cases were found in only one source. Most of these cases (67%) were identified from hospital inpatient records. While 25% of cases were ascertained from more than one source, only 4% were not found in hospital records.

Table 11 presents the reviewed records by gender, age, and race/ethnicity. About 75% of cases were female. The number of cases was highest among the 40-49 year old and 50-59 year old age groups (28.8% and 26.4%, respectively), accounting for more than 50% of cases. The number of cases was lowest in the <30 age group (7%). The occurrence of MS by race/ethnicity was unknown because more than 71% of the records reviewed had either no race/ethnicity information indicated or the information was unclear.

Table 12 shows the number of cases reported from secondary sources. As with ALS, these cases were used to assess the accuracy of prevalence estimates using primary source data only. There were a total 250 individuals for whom a report was received from a secondary source, which indicated a diagnosis of MS prior to 2004 in individuals who had resided within the surveillance area and had not previously been identified from a primary source. The Rhode Island Naval Hospital data suggested that up to 37 MS cases were not identified from other primary data sources and may have met the study case definition. Most of the deaths due to MS were not reported from primary sources (90%). Similarly, a majority of patient advocacy group cases (58%) and community advocacy cases (55%) were not reported from primary sources.

For analyses comparing prevalence with a reference area, only cases with a physician's visit between 1998 and 2001 were used so that the surveillance period of both the study and reference areas was the same. As shown in Figure 2b, there were 711 cases identified for this time period. Similarly, for analyses of the 3-town area, there were 177 cases who were residents of Abington, Rockland, or Weymouth and had seen a neurologist between 1998 and 2003 and 135 cases identified for the 1998-2001 period (Figure 2b).

4.4 Prevalence of MS

Prior to verification of diagnosis, the overall period prevalence of MS for the full Southeastern Massachusetts study area for 1998-2003 was estimated at 147 per 100,000 population based on the 800 cases ascertained. Similarly, the prevalence estimate for the 3-town area before verification was found to be 205 per 100,000. Appendix 7 presents the period prevalence for each individual town in the study area. The range of prevalence by community was 21.8 per 100,000 in Rochester to 220.3 per 100,000 in Hanover. The confidence intervals for all towns were wide indicating that these community-specific estimates were not precise because of the small numbers of cases within each municipality.

As with ALS, an objective of the project was to estimate prevalence based on cases whose diagnosis was verified through the application of standardized diagnostic criteria. A sample of 90 case records was selected for review by a neurologist for verification. As discussed in the Methods section, two different diagnostic criteria were applied. The initial step was to compare the results of applying the two diagnostic criteria to the same records. Table 13 shows the results of this effort. A similar percentage of reviewed cases met the Poser and McDonald criteria for a definite diagnosis of MS (66% and 71%, respectively).

The same records were not necessarily characterized as definite/probable MS by both the Poser and McDonald diagnostic criteria. Following the assessment of any differences, Table 14 shows that the overall percentage of reviewed records that met both criteria for a definite or probable diagnosis was 70.0% (n=63). Agreement was also reached in categorizing about 4% of cases as not MS (n=4). The diagnosis of about 12% of cases was considered to be indeterminate (n=11) because of insufficient clinical information. Agreement was not obtained for the remaining 13% of records. Since only a sample of cases were verified, the verification percentage (i.e., 70%) was subsequently used to estimate the number of definite and probable

MS cases from the total number of cases ascertained from medical records. These figures were subsequently used to estimate prevalence in all study populations and time periods.

The number of cases estimated to be definite or probable MS for the full study population of 800 cases identified and for full surveillance period (1998-2003) was 560 (refer to Figure 2b). The number of estimated for 1998-2001 it was 498. The number of verified cases estimated in the 3-town area was 124 for 1998-2003 and 94 for 1998-2001.

Table 15a presents the estimates of MS period prevalence for the total study and reference areas based on verified diagnoses. Because there is no nationwide surveillance of MS, the reference estimate used is an approximation for northern latitudes based upon published scientific studies. The reference study was based on a 4-year prevalence period (1998-2001), thus, prevalence for Southeastern Massachusetts was also estimated for a 4-year period (1998-2001). The prevalence estimate shown for Southeastern Massachusetts includes only those cases with either a verified diagnosis of definite or probable MS, since only those diagnoses were included in the reference study. The 4-year prevalence for the total study area was estimated at 91 per 100,000 (95% CI 84-100). The period prevalence estimate applied for the reference area (Neuberger, 2004) was 115 per 100,000 (95% CI 97-135). The prevalence ratio for the comparison of the full study area with the reference study was 0.79 (95% CI 0.66-0.95). This ratio indicates that the prevalence in the study area was statistically significantly lower than the reference area.

Table 15b presents a chart showing how period prevalence might vary if some cases reported as MS but not reviewed for verification were definite or probable MS. The estimates are based upon the full 6-year surveillance period. The case category 1 estimate shows the estimate of prevalence for verified cases from primary sources only. This category represents the most reliable estimate because it is based on verified diagnoses only. The estimate was 103 per 100,000 with a lower confidence limit of 94 and higher confidence interval of 111. Case category 2 assumes that some reported cases from patient advocacy groups, death certificates, and cases from primary sources whose diagnoses could not be verified due to incomplete clinical records (including cases from the RI Naval Hospital) are definite or probable MS. In order to estimate the number of total cases with incomplete records, the sample of record reviews was used, as it was to estimate the verification percentage. From the sample of records reviewed, it

was estimated that about 14% of cases had incomplete records. This value of 14% was applied to the total number of reported cases (n=800) and the result was an estimate of 115 cases with incomplete medical records. If the verification percentage of primary cases (70% - refer to Table 14) is applied to these cases, then 255 additional “verified” cases can be assumed (i.e., 70% of cases from the 250 secondary source cases and from the 115 non-reviewed primary source cases), resulting in a period prevalence of 149 per 100,000 (95% CI 139–160). Case category 3 represents the maximum prevalence and assumes all 250 secondary source cases and 115 non-reviewed primary source cases are definite or probable MS (170 per 100,000; 95% CI 159-181).

Similarly, a 4-year prevalence estimate was also determined for the 3-town SWNAS study area (Abington, Rockland, and Weymouth) and this estimate was compared with both the reference area and the total study area prevalence (Table 16a). This 3-town area estimate was 109 per 100,000 (95% CI 89-133). The prevalence ratios for the comparison of the 3-town SWNAS area with the reference study and the full study area were 0.95 (95% CI 0.73-1.23) and 1.20 (95% CI 0.96-1.49), respectively. Although the ratios suggest that the prevalence of MS was higher in the 3-town area than the total study area (20% higher than the total study area) and somewhat lower than the reference area, neither of these differences were statistically significant.

Table 16b presents a chart showing how period prevalence for the 3-town SWNAS area might vary if some cases reported as MS but not reviewed for verification were definite or probable MS. The estimates are based upon the full 5-year surveillance period. The estimate of 144 per 100,000 (95% CI 120-171) represents the minimum prevalence of MS in the study population, based upon 124 cases who were residents of the 3-town area, and is the most reliable estimate because it is based upon verified diagnoses only (case category 1). Case category 2 assumes that some reported cases from patient advocacy groups, death certificates, and primary source cases that could not be reviewed for verification of diagnosis (including RI Naval Hospital cases) are definite or probable MS. If the verification percentage of primary cases (70.0% - refer to Table 14) is applied to these cases and this assumption is true, then 44 additional “verified” cases can be assumed (i.e., 70% of the 63 cases from secondary sources and non-reviewed primary source cases who were residents of the 3-town area – refer to Figure 2b), resulting in a period prevalence increased from 144 to 195 per 100,000 (95% CI 167-226). Case category 3 represents the maximum prevalence and assumes all secondary and non-reviewed

primary source cases who were residents of the 3-town area are definite or probable MS (217 per 100,000; 95% CI 188-250).

A further statistical analysis was done to see if there was clustering of MS near the SWNAS. For this analysis, 781 of the 800 primary source cases had information on the address location that could be used. Figure 4 gives a visual display of the prevalence of MS per 100,000 and the location of the SWNAS. Two statistical methods were applied to evaluate the spatial clustering in Southeastern Massachusetts. The first was the Spatial Scan Statistic (SATScan v6.0), which found significant clustering of MS near the SWNAS even after adjusting for gender with a p-value of 0.032 (Figure 5).

The second statistical method was the Cumulative Geographic Residuals Test (CumGeoRes). The results are depicted in Figure 6 with the statistically significant MS cluster (p-value=0.05) that corresponds to an area that surrounds the SWNAS.

The relationship between the location of case residences and distance to the SWNAS boundary was also assessed. Results found that there is a 29% higher prevalence of MS (95% CI 1.03-1.61) in the “Within 2 KM” cluster area and the same 29% higher prevalence (95% CI 1.02-1.65) was estimated in the “2 to 5 KM” cluster area compared to prevalence in the rest of the study area. In other words, while MS prevalence is significantly higher around the SWNAS, it appears similarly higher at distances further from the base. If residential proximity to the SWNAS played a primary role in the prevalence of MS, we would expect to see greater numbers closer to the base. Instead, the numbers dropped.

The grouping of cases within the 3 communities was also visually assessed to determine if there are certain geographic areas where more cases appear to reside at time of diagnosis. The cases were clearly located in areas of higher population density with most in areas more than a half mile from the base boundary. Cases within a half- mile were not grouped together in numbers or pattern differently than observed in any other areas of the communities.

5.0 Discussion

5.1 ALS

The objectives of the study included estimating the number of ALS cases from hospital and physician medical records, verifying which cases had a diagnosis of definite or probable ALS, determining if the prevalence of definite and probable ALS in the study area was statistically significantly different from prevalence reported in the scientific literature, and determining whether the geographic distribution of cases suggested that environmental factors might play a primary role in the observed prevalence. Prior to the start of the surveillance project, the number of cases expected was estimated based upon the 2000 Census population data for the study area and published estimates of prevalence. A prevalence of 4 to 6 cases per 100,000 population was assumed for ALS of any type diagnosis for the year 1998 (Roman 1996; Proctor et al. 1992). The annual incidence rate for ALS is approximately 2 new cases of ALS per 100,000 population (McGuire et al. 1996). For the study population of approximately 500,000, this translated to estimates of 20 to 30 prevalent ALS cases at the beginning of the surveillance period and about 10 new cases each year of surveillance (prevalence is based upon both existing cases and newly diagnosed “incident” cases). However, the total number of cases observed with a reported diagnosis of ALS was 43, with another 56 cases from secondary sources. The observed numbers are just slightly greater than what was expected.

A more precise determination of whether the observed prevalence of ALS in Southeastern Massachusetts was unusual was carried out by statistically comparing prevalence estimates for the study area with that for a different geographic area outside of Massachusetts, which used similar surveillance methods. Based on the scientific literature, the expected point prevalence in similar studies ranged from 3.9 to 4.7 per 100,000 (Traynor 1999, Mandrioli 2003, and Turabelidze 2008a). These estimates were based on relatively small numbers of cases in small populations, therefore, their point estimates cannot be considered precise.

In this study, the point prevalence estimate based on the reported diagnosis by medical providers was 5.5 per 100,000 (i.e., the prevalence of cases living December 31, 2003 and prior to verification of diagnosis). It was found that only about 44% of these cases reported as having an ALS diagnosis were verified as having definite or probable ALS. Following the verification of diagnosis and limiting prevalence to only verified diagnoses of definite or probable ALS, the

prevalence estimate determined was 2.4 per 100,000 (95% CI 1.3-4.0). Although the value appears lower than the value for the reference area (3.9 per 100,000; 95% CI 2.0-7.7), this estimate was not meaningfully different from either the estimates reported in the scientific literature or in statistical comparison with the reference area because they are based on small numbers with wide confidence intervals.

The prevalence by gender was slightly different from seen nationally. Published studies have suggested that males have a slightly greater prevalence than females (Armon 2001). In Southeastern Massachusetts, more females than males had a diagnosis of ALS (53.5% compared to 46.5%). However, the number of cases was small and there was no statistically significant difference in the prevalence between males and females. The number of cases by age were distributed as expected, from the literature with almost all cases occurring in the 50 to 70+ age group. The race and ethnicity of cases was not available for almost 80% of cases. This was largely due to missing information or the use of hospital codes that did not differentiate between Hispanic and non-Hispanic race.

While the point prevalence estimate based on verified cases (2.4 per 100,000) was not statistically significantly different from the reference prevalence (3.9 per 100,000), the study included the reports of ALS cases from secondary sources, such as patient advocacy groups like the ALSA, which could not be included in the point estimate because their medical records could not be reviewed to verify their diagnoses. This raised the question of whether prevalence based on verified primary source cases only could be an underestimate.

The surveillance of ALS in Southeastern Massachusetts was carried out in cooperation with both the medical community and patient advocacy groups serving the area. All hospitals and neurology practices contacted participated in the surveillance effort, with the exception the Veterans Administration (VA) Hospital in West Roxbury, Massachusetts. All but 4 of the 43 cases identified were found through the review of hospital inpatient and clinic records (4 cases were identified through private neurology practices). However, medical records for 1 case reported by the Naval Hospital in Rhode Island and 9 cases reported by other primary sources whose records contained incomplete clinical data, such as missing reports on disease progression or electromyography (EMG) results, could not be reviewed to verify if the patient had definite or probable ALS. Additionally, the cases identified from primary sources were compared with

cases provided through the secondary sources. There were 6 cases reported by advocacy groups as meeting the case definition but that had not been reported by any primary case sources. The medical records of these cases also could not be reviewed to verify diagnosis. It seems reasonable to assume that at least some of the cases from secondary sources may be definite or probable ALS since they were reported as meeting the study's eligibility criteria. If this assumption is true, then it is likely that the estimate based on verified cases only in this study (2.4 per 100,000) represents an underestimate of prevalence. In order to assess the possible impact on our prevalence estimate, we applied the same verification percentage found with cases reported from primary sources to all secondary source cases and primary source cases whose records were incomplete. We found that the prevalence increased from 2.4 to 3.1 per 100,000. It is possible that not all of these cases would be verified at the same rate as the primary source cases. For example, the cases with incomplete records may have incomplete records because clinical work-ups were not done due to physician doubts in the diagnosis. However, it is an important observation and limitation in this study that, because all records of reported cases could not be reviewed, the calculated prevalence value may be imprecise. It is also important to note, though, that the full range of possible prevalence for Southeastern Massachusetts that we explored was not meaningfully different from that presented in the scientific literature for the general population. Therefore, even if the assumption of underestimation of prevalence based on verified diagnoses is true, the occurrence of ALS in Southeastern Massachusetts for the study period does not appear elevated, even if prevalence is based on the total number of cases reported from all sources.

Comparison of the reference area with the study area should also be interpreted with caution because it likely is affected by the small number of cases that the reference population represented. This results in an imprecise reference estimate making differences between the reference and study estimate difficult to detect or interpret. The statistical comparison is nevertheless helpful in placing into perspective the prevalence estimates obtained, since the comparison had the intended purpose of addressing concerns about elevated prevalence due to environmental exposures. However, the reference prevalence estimate was part of an investigation that detected an ALS cluster in an area of possible environmental exposures (Turabelidze 2008a). It therefore is possible that this reference estimate might be somewhat

higher than if the estimate had been generated in a population confirmed to be “non-exposed”. If the reference estimate is itself somewhat elevated due to some environmental exposure, then it may have the effect of biasing the comparison with our surveillance estimate in the direction of not finding a statistically significant difference when one might actually exist.

The environmental analysis was conducted based upon all primary source cases since these were the cases with sufficient demographic information and for which the medical record clearly indicated was a diagnosis of ALS. No cases that met the study case definition were identified among residents of Middleborough, the area of concern to residents because of a previous history of suspected higher prevalence. For that reason, no special environmental analyses examining the clustering of cases could be conducted. [Note: MDPH is conducting environmental health consultations of the Gerson Properties and Middleborough Plating sites for ATSDR to address environmental concerns]

5.2 MS

The objectives of the MS surveillance were the same as for ALS; estimating the number of MS cases from hospital and physician medical records, verifying which cases had a diagnosis of definite or probable MS, determining if the prevalence of definite and probable MS in the study area was statistically significantly different from prevalence reported in the scientific literature, and determining whether the geographic distribution of cases suggested that environmental factors might play a primary role in the observed prevalence. There are no MS registries to provide a statistically stable estimate of prevalence in Massachusetts’ communities or elsewhere. However, surveys, such as the National Health Interview Survey (NHIS), have enabled national prevalence estimates to be made. The NHIS estimated overall prevalence in the US to be 85 per 100,000. Other studies have revealed that northern latitude areas in the US and around the world have consistently higher prevalence at 110 to 140 per 100,000 (MS Society 2002B). Some studies, such as those discussed by Noonan (2002), report prevalence up to 173 per 100,000. Prior to the start of the project, the total number of cases of MS expected in the surveillance area over the full study period was approximately 600 to 764. This was based upon an expected northern latitude prevalence of 110 to 140 cases per 100,000 (National Multiple Sclerosis Society 2002b) and assumes an annual incidence of 6 cases per 100,000 (Weinshenker 1996; Jacobson et al. 1997). The 800 cases identified from medical records reports prior to

verification gave a period prevalence estimate of 147 per 100,000 for the full surveillance period, which was slightly greater than expected.

In order to determine if the prevalence of MS was higher in Southeastern Massachusetts, comparisons of prevalence based on verified diagnoses of MS was necessary. Following the review medical records for a 10% random sample of the 800 reported cases, it was estimated that 70% of reported cases were verified as definite or probable MS. When only cases verified as definite or probable diagnoses are considered, the period prevalence estimate for the full surveillance period was 103 per 100,000 (95% CI 94-111), based on 560 cases. Similarly, period prevalence was also estimated for the 3-town area abutting SWNAS (Abington, Rockland, and Weymouth). The estimate based on 124 verified cases for the 3-town area was 144 per 100,000 (95% CI 120-171).

The interpretation of whether a prevalence estimate is higher than expected requires statistical comparison with an estimate based on the same surveillance methodology. This is only possible when restricting the comparison to estimates based on verified diagnoses. A study by Neuberger (2004) employed methods similar to those used in the Southeastern Massachusetts study, except advocacy and some other secondary sources of cases were not used by Neuberger. The reference study prevalence estimate was 115 per 100,000 (95% CI 97-135) for a 4-year period. It was necessary to generate a prevalence estimate for the total and 3-town study areas that represented the same 4-year prevalence period as the Neuberger study. That time period was 1998-2001 and the prevalence for that time period was estimated as 91 (95% CI 84-100) and 109 per 100,000 (95% CI 89-133) for the total study area and 3-town study area, respectively. Comparison of the total study area prevalence with the reference area prevalence was statistically significantly lower than in the reference population. Comparison of the 3-town area prevalence with the reference area prevalence did not suggest that the estimates were statistically significantly different. Comparison of the 3-town area prevalence with the total study area prevalence also was not statistically significant, though the 3-town area prevalence was higher than that of the total study area. This finding is further discussed below.

Prevalence among females in the total study area was almost 3 times greater than that among males, with a female to male ratio of 2.9 to 1. This is similar to that reported in the literature where the ratio was 2.6 to 1 (Noonan et al. 2002). The age distribution of cases found

through this surveillance also corresponded to that reported in the literature. Noonan et al. (2002) stated that prevalence was highest in the 40-59 year old age group. In Southeastern Massachusetts, the highest prevalence was also in the 40-59 year old age group. As with ALS, race and ethnicity information was not available for a large proportion of MS cases (71%).

There were a sufficient number of cases for additional analyses to evaluate the geographic distribution of cases within the towns abutting the Naval Air Station. After applying two statistical cluster detection methods, it was concluded that there is evidence of a higher prevalence of MS in communities that abut the South Weymouth Naval Air Station compared with the rest of the study area. However, analyses of the distance of MS cases from the base did not find that the number of MS cases increased as proximity to the Naval Air Station decreased. Most cases were located in areas of higher population density and not adjacent to the base boundary. Those that were residing closer to SWNAS were not grouped together in a pattern or number of cases that were different from that seen elsewhere in the communities.

These observations do not suggest a conclusion that some particular factor related to the SWNAS is associated with the prevalence of MS in the area. Other predictors of the relationship, such as other environmental or occupational exposures and medical and residential histories, would need to be evaluated to identify potential factors that may allow for a clearer understanding of the increased prevalence of MS in these communities. Additionally, prevalence could be higher near the base because of a younger age distribution for Weymouth, Abington, and Rockland and/or greater migration in and out of the area (i.e., resulting in more cases because migration results in a greater population and pool of potential cases). In order to provide a crude evaluation of the possible validity of the migration factor, U.S. Census data for 2000 were considered and they indicated that Norfolk County (the location of SWNAS), had an in-migration rate between 1995 and 2000 of about 7.78%, while Plymouth County (the location of most of the study area) had an in-migration rate of 5.3%. Since MS cases were ascertained on an ongoing basis during the study period, the higher in-migration suggests that the pool of potential MS cases might change during the course of the study period due to migration and artificially increase the number of cases for the 3-town area. This could artificially elevate the MS prevalence estimate because, while the cases may increase during the study period, the population numbers used in the calculation do not account for any increased population due to

migration and so remain at the same level for the full study period. For an estimate to accurately include new cases due to migration, the population for the communities must also include the new population.

Another factor that suggests that the increased number of cases near the SWNAS should be interpreted with caution is the analytic assumption that each diagnosis occurred after residing in the study area. It is likely that at least some cases were diagnosed prior to moving to the study area but these individuals could not be readily identified using data available in medical records. This is because address may be missing from older records or overwritten in electronic records. Since the cluster analysis took into consideration cases throughout the study area in order to detect clustering, cases that might be ineligible due to diagnosis prior to residence could artificially enhance the statistically significant differences reported.

As with ALS, the potential for under-ascertainment of MS and the underestimation of prevalence was evaluated.

Cases may have been under-ascertained because some private practice neurologists outside the study area were not contacted. Although most MS cases were identified from hospital records, unlike ALS, at least one third of the cases were only identified from private practice neurology offices. Moreover, unlike ALS, about 20% of the cases were identified in multiple hospital and/or neurology physician sources. This observation seems reasonable considering that the disease generally has a long-term survival and hospital stays are not often required during the course of the disease. While it seems unlikely that a significant number of patients would seek ongoing care at a neurologist office in Boston (other than at an MS clinic or hospital), more than 100 cases were reported by the MS Society that were not reported by a primary source. This may suggest a possible missed source of cases or that some cases were not seen by a neurologist during the 6-year study period.

Cases reported by patient and community advocacy groups but not by neurologists may suggest some cases were under-ascertained using only hospital and private neurologists. Nelson and Anderson (1995), report that patient advocacy and service organizations can be high-yielding sources for ascertaining cases. In two surveys they reviewed, 51% and 53% of cases were identified by this method. They point out that, particularly for MS patients whose condition has not required medical attention in recent years, client lists from these organizations

may be the best way to identify these cases. Although, patient advocacy groups appear to be a valuable data source for surveillance, the proportion of MS cases potentially ascertained through patient advocacy groups in Southeastern Massachusetts was about 13%, which is significantly less than Nelson and Anderson found. Without reviewing each of these records, it is not possible to determine if each met the case definition.

A community advocacy group, AWARES, provided the names of individuals who lived or had lived in the communities surrounding the SWNAS and who self-reported a diagnosis of MS. There were 77 individuals identified and information was requested for these cases by project staff on the date of birth, address, and diagnosis to help determine if they met the case definition. There were 35 individuals who provided information that could be confirmed as meeting the case definition. However, more than 50% of the individuals reported did not have the requested information necessary to allow confirmation of the case. Therefore, it is not known if the cases reported to AWARES with missing information were eligible cases.

The number of deaths due to MS that were not identified through primary sources is another factor suggesting case under-ascertainment. As with ALS, a number of deaths with MS as an immediate or underlying cause were found (n=58). Only about 10% had also been identified through the primary data sources. It could not be determined if these cases met the case definition. The medical records could not be reviewed for the patients not already identified to determine if they were a missed case or a case with a residence or date of physician visit outside of the eligibility criteria.

Cases may have been under-ascertained because of being diagnosed/treated out-of-state. The MDPH MS/ALS Advisory Group suggested that some cases might have been missed if they were in the employ of the U.S Navy at the SWNAS or a dependent of someone who was. If so, diagnosis and treatment could have taken place at the Rhode Island Naval Hospital. Inquiries to the hospital resulted in 42 cases being identified by the Navy with only 5 having been previously identified through the primary data sources (11.9%). Although the records of these cases could not be verified, the number of reportedly eligible cases suggest that these out-of-state cases may have contributed to an underestimation of prevalence based only on verified cases.

Prevalence may have been underestimated because of the method of verification of diagnosis used in this study. Unlike ALS where all records from primary sources were reviewed,

only a 10% random sample of the 800 MS records were reviewed. Two sets of diagnostic criteria had been applied in the review of the 90 record sample by the project neurologist. The Poser method classified about 80% of the cases as definite or probable MS. The McDonald method classified about 71% as definite MS (probable was not selected by the neurologist as a category of diagnosis). This difference may be due to the McDonald method's greater reliance on magnetic resonance imaging (MRI). Overall, agreement between the two methods was 70% for definite or probable MS.

Prevalence may have been underestimated because the number of verified definite and probable MS cases was based on a sample of reviewed records (for ALS, all cases from primary sources were selected for verification). Although verification of a definite or probable diagnosis was much greater for MS than for ALS cases, it was found that if verification was restricted to cases with physician visits during different years (e.g., 1998-2001), the percent of cases verified with definite or probable MS increased from 70% to 82%. While this was based on an even smaller number of records (n=78), it makes the observation that the verification percentage may be imprecise or variable, even though attempts were made to sample similarly from each clinic/office in order to minimize geographical or physician bias. This imprecision was likely further contributed to by the approximately 14% of MS records reviewed that were found to be incomplete and, therefore, not able to be verified.

Prevalence may have been underestimated because of primary source cases whose records could not be reviewed. Although all primary source cases were not confirmed cases, many of the remaining cases were classified as an indeterminate diagnosis because of inadequate clinical information, such as missing laboratory and MRI results. It is possible that some of these may likely be definite or probable cases since the medical records of each included a clear statement of diagnosis and the diagnosis of about 70% of other primary source cases whose records could be reviewed were verified. However, it is also possible that verification percentage for these cases may be different from that observed for other primary source cases. It is unknown why the medical records were incomplete. Information used to diagnose the patient may not have been located because some cases had been diagnosed many years prior to the study. Laboratory or MRI scans may not have been conducted because the physician did not believe the patient had definite MS.

Because of the possible impacts of under- and over-ascertainment of MS cases on prevalence, the prevalence of MS that was estimated may be imprecise. We attempted to assess the possible impact on prevalence by applying the verification percentage found from reviewing the records of the sample of primary source cases on the number of secondary source cases plus primary source cases whose records could not be reviewed because they were incomplete. We found that for the 1998-2003 period, the prevalence increased from 103 per 100,000 to 149 per 100,000. Prevalence could be as high as 170 per 100,000 if all secondary source cases and incomplete primary source cases were definite/probable MS. However, this latter scenario is unlikely, especially since the figure includes cases reported from death certificates for which both study eligibility and verification of diagnosis were in question. Although the 70% verification rate may not apply to the secondary source cases, it seems reasonable to assume that some secondary source cases and incomplete primary source cases could be definite or probable cases since they were reported as MS diagnoses. Therefore, it is reasonable to assume that the prevalence estimates for the total study area were underestimates. Nevertheless, if this assumption is true, none of the possible estimates of prevalence for Southeastern Massachusetts would be meaningfully different from what would be expected based upon published data on the prevalence of MS in the general population.

Prevalence in the 3-town area for 1998-2003 was found to be higher than in the study area as a whole. Statistical comparisons with the total study area and the reference area for 1998-2001 found no statistically significant differences in prevalence, other than those of the statistical cluster analyses discussed earlier. However, as presented with regard to the total study area, the possible under-ascertainment of cases could also have resulted in an underestimation of prevalence for the 3-town area. After apply the verification percentage for primary source cases to the number of cases among residents of the 3-town area, the prevalence estimate was seen to increase from 144 per 100,000 to 195 per 100,000. While it cannot be said that the verification percentage applied for the secondary source was valid, it appears reasonable to assume that some of these cases may be definite or probable MS. Importantly, if this assumption is correct, the prevalence estimate based only on verified cases from primary sources may be imprecise and prevalence for Southeastern Massachusetts could be higher than what the published literature

suggests for the general population. However, this conclusion cannot be confirmed or quantified since the verification of all records would be necessary.

It is possible that comparisons in prevalence with the reference population may be underestimated. For both MA and ALS the reference prevalence estimate was selected because the reference studies applied comparable data collection methods. The comparisons conducted in this study assumed that the reference population does not have meaningful exposures that could impact prevalence. If the reference population was potentially impacted by such exposures, then differences in prevalence between the study and reference populations could be greater than observed because of exposure bias. However, because prevalence estimates from studies using comparable methods are limited, the study from which the MS reference estimate was drawn was conducted in order to investigate impacts of possible environmental exposure. Although this study detected no impacts on the prevalence of MS, it is important to note that a major limitation of reference data based on small numbers is potentially more susceptible to biases such as exposure bias.

5.3 Strengths and Limitations

The major limitations of this surveillance project are those inherent in any descriptive or ecological study, where information on personal risk factors is not collected. There was no interviewing of cases or controls to obtain personal risk factor information such as residential or occupational history or exposure-related information on individuals. Further, the “ecologic fallacy” comes into play - that is, cases under surveillance are assumed to possess characteristics of the group when in fact they, as individuals, may not possess the characteristic. Our analyses were limited to evaluating *proximity* to an area of environmental concern, as a proxy measure not potential *exposure* to actual environmental contaminants in the development of MS or ALS. This surveillance project was designed to evaluate available health data to estimate how much ALS and MS was present in Southeastern Massachusetts. Further, the results of the GIS analysis were intended to generate hypotheses for further study not causal inference. In fact, it is not possible to examine, in this type of surveillance project, the temporal relationship between exposure and the onset of disease without knowing full residential history information and, of utmost importance, whether residence in a given community preceded disease.

In the surveillance area, the number of cases of ALS during the surveillance period was relatively small. Therefore, statistical comparisons of ALS prevalence in different geographic areas in the limited time period of the study were not possible.

Methodological limitations included the lack of clinical data for some cases resulting in an inability to verify their diagnosis. Often, the lack of data was manifested as a limitation of data abstraction where sufficient detail was not always available. A possible solution might be the photocopy of key clinical information, such as EMG results, for ALS cases. Also observed was a possible under-reporting of cases that had died during the study period. The study was unable to verify the cases identified from death certificates and patient advocacy groups, though these cases seemed to meet some case eligibility requirements. Analytic limitations included the small number of ALS cases, which restricted the ability to evaluate the clustering of cases. In addition, only period prevalence estimates were made for MS because of the limited availability of point prevalence estimates using similar methods as those used in this study. For both ALS and MS there was a limited selection of appropriate reference prevalence estimates. Period prevalence estimates of ALS could not be identified and only three point prevalence estimates could be identified that incorporated methods similar to this study. Point prevalence estimates for MS in the literature using methods similar to those in this study could not be identified. As a result, the two diseases investigated generated different types of prevalence estimates. This enabled appropriate comparison with reference estimates but complicated the presentation of findings. Interpreting period prevalence for MS also was made difficult because period prevalence does not allow for the control of population migration that some available census data suggests varied within the study area and could have affected prevalence comparisons within the study area (including the 3 communities surrounding the SWNAS).

The use of multiple case-finding methods for this surveillance project represents a strength of the surveillance design. Understanding the merits of the various data sources is helpful if surveillance is expanded or applied to other populations. In this study, most health professionals reported cases from specialty clinics, hospitals, or HMOs. However, a number of cases were reported from secondary sources, including death certificates and patient advocacy groups. It is possible the cases only reported through death certificates are the result of health professionals only reporting living cases. It is unclear at this time, however, why cases from

advocacy groups were not also reported by health professionals, given that patients/families reported, by way of a consent form, information on a diagnosed case, including date of physician visit and residence within the study area.

The overall limitation of this study related to the imprecision of the prevalence estimates due to the suspected under-ascertainment of cases. The additional cases identified from secondary sources and the records for some primary source cases that could not be reviewed to verify diagnosis, limited the study's ability to determine a precise estimate of prevalence for ALS or MS.

The statistical methods employed in this study are particularly useful for interpreting the relative magnitude of ALS and MS prevalence in Southeastern Massachusetts and the relative differences in prevalence estimates between populations in different geographic areas. Given the concerns about incomplete case ascertainment from primary sources in the Massachusetts ALS/MS study (and likely in the reference studies), a major strength of this study is in its approach to comprehensively ascertain ALS and MS cases and contribute to a more complete understanding the occurrence of ALS and MS in Southeastern Massachusetts than was previously known.

5.4 Surveillance Lessons Learned

The results of the Southeastern Massachusetts study revealed several important lessons regarding what defines a successful ALS and MS surveillance system.

1) Because the diagnosis of both ALS and MS is complicated and can involve continual medical testing and evolving medical opinion, there was an expectation that not all patients reported as ALS and MS cases through ICD codes and statements of individual physician impressions would be verified with a definite or probable diagnosis, regardless of the source. This study confirmed this expectation and reinforced the premise that successful surveillance and incidence/prevalence estimation would seem to require a diagnostic verification component utilizing standardized diagnostic criteria rather than acceptance of ICD codes and medical record conclusions for at least some cases. In addition, because of the natural history of ALS and MS, consideration should be given to the periodic re-review of records of the many cases that may progress from a diagnosis of possible or suspected diagnosis to a definite or probable diagnosis, which could further influence prevalence if not accounted for.

2) Multiple sources of potential cases can be a key surveillance component, particularly at the start of a new surveillance effort. Secondary sources such as patient advocacy groups and death certificates may be helpful in identifying cases not initially reported by neurologists. As surveillance reporting requirements become more familiar to health providers, the role of secondary sources may be reduced. Future surveillance efforts by researchers or public health departments should consider additional sources of cases not employed in this project. These include Medicaid/Medicare records and nursing home/hospices. The consideration of the usefulness of these data sources as secondary sources in the evaluation of surveillance methods or as primary data sources, in the case of Medicaid/Medicare data, would provide further insight into what the essential components of an ALS/MS surveillance effort should be.

3) A number of medical records were insufficient for diagnostic verification. In this study, this potentially resulted in imprecise estimates of prevalence. However, the study learned that the necessary clinical data for both primary and secondary sources is most always available but requires the commitment of sufficient resources for adequate follow-up through multiple provider visits in order to locate the record of the diagnosing physician. This task would be expected to be less problematic the more recent the date of diagnosis.

4) While the information collected from providers requires careful review in order to abstract the necessary demographic and clinical information, it was most always reliably available when the record of the diagnosing physician was located. Race and ethnicity information, however, was uniformly of poor quality if available at all. These variables, along with geographic information, potentially provide important demographic descriptions of the patient populations. Some states are currently informing and training hospital and health provider personnel on the requirement and methods for obtaining reliable race and ethnicity information on a patient. This instruction is necessary so that race and ethnicity can be uniformly collected in accordance with guidance provided by the U.S. Office of Management and Budget (OMB).

5) Federal databases with personal identifiers, such as those from Veterans Administration hospitals, are not readily available for review. Permission to access these records requires much planning.

6) The Southeastern Massachusetts surveillance project identified the important sources for cases and the necessary clinical information for determining definite and probable ALS and MS cases. Further work by the MDPH is continuing to delineate the best methods for ongoing/prospective surveillance of ALS. In Section 26 of Chapter 140 of the Acts of 2003, the Massachusetts legislature directed that “the Department of Public Health shall establish an ALS registry, by areas and regions in the Commonwealth, with specific data to be obtained from urban, low and median income communities, and minority communities of the Commonwealth.” A statewide ALS Registry was initiated in January 2008 for prevalent cases beginning in 2007.

Prior to initiation of the Registry, several activities were conducted to build upon the lessons learned in this study. The activities included pilot surveillance studies in Essex and Suffolk (Boston) Counties. The framework for the pilot studies was an extension of the Southeastern Massachusetts surveillance project. The goals of the pilot studies were to further develop registry designs and implementation strategies, and to explore implications for reporting, identifying and tracking clinical and other data, costs, required information technology resources, and legislative and other key administrative issues.

The ALS pilot efforts conducted by the MDPH have noted the longstanding interest and support of a number of ALS clinicians, patients, and their families (e.g. the ALS Association) in developing standards and procedures for a patient registry and for follow-up studies to facilitate the understanding of the causes and treatments for this disease. Statewide surveillance systems rather than regional registries or sample surveys are considered necessary in order to better establish the true prevalence of the disease and to facilitate follow-up studies of patients. An ALS registry can also be an important support for future decision-making related to the prevention and treatment of the disease.

As other states may develop or consider development of a statewide or national registry for ALS, the Massachusetts Registry, as the first state to establish a population-based registry, could serve as a valuable resource.

6.0 Conclusions/Recommendations

6.1 ALS Prevalence

The point prevalence estimate of verified definitive/probable diagnoses of ALS in Southeastern Massachusetts in December 31, 2003 was 2.4 per 100,000 (95% CI 1.3-4.0). Of the 43 cases from reported by health professionals, only 19 were verified as definite or probable ALS following the application of standardized diagnostic criteria. Prevalence did not appear to be elevated in Southeastern Massachusetts. Statistical comparisons of prevalence are only appropriate for verified diagnoses of definite or probable ALS. The comparison with a reference estimate by Turabelidze (2008a) in Missouri (3.9 per 100,000; 95% CI 2.0-7.7) concluded that the prevalence of ALS in Southeastern Massachusetts was not statistically significantly different from the reference area. Meaningful analyses by individual community and particularly for Middleborough, where exposure to hazardous waste sites was suspected, were limited due to the small numbers of cases in each community. Of the 30 study communities, 19 had less than or equal to one case identified. Middleborough had no diagnosed ALS cases among its residents between 1998 and 2003. The number of ALS cases in the communities surrounding the SWNAS seemed higher than in other areas, but the number was too imprecise to assess statistically.

However, the results of this project suggest that this prevalence value may be underestimated. Some cases, reported as meeting the case definition by medical providers/neurologists, had incomplete records and a small number of additional cases from secondary sources, such as patient advocacy groups, could not be included since their medical records could not be reviewed to verify their diagnosis. When the percent verification of definite and probable ALS from primary source cases was applied to the reported cases whose medical records could not be reviewed, point prevalence for the study area was estimated to be between 2.4 per 100,000 and 4.0 per 100,000. This range of prevalence was still not higher than what would be expected for the general population based on prevalence estimates reported in the scientific literature.

6.2 MS Prevalence

The period prevalence of verified definitive/probable MS in the total study area was estimated to be 103 per 100,000 (95% CI 94-111) for the full surveillance period (1998-2003). There were 800 cases identified from health professionals. Based on verification of a random

sample of these cases, 70% were estimated to be definite or probable MS after application of standardized diagnostic criteria. Prevalence did not appear elevated in Southeastern Massachusetts. Similarly, the prevalence based on verified diagnoses for the 3-town area surrounding the SWNAS was 144 per 100,000 (95% CI 120-171) for the full surveillance period.

Statistical comparisons of the prevalence estimates for the total study area and the 3-town area were made to the reference estimate generated by Neuberger (2004) in Kansas (115 per 100,000; 95% CI 97-135) and limited to the same prevalence period as was used by Neuberger (i.e., 1998-2001). The prevalence estimate for this 4-year period for the total study area was 91 per 100,000 (95% CI 84-100) and for the 3-town area was 109 per 100,000 (95% CI 89-133). The statistical comparison to the reference area indicated that prevalence in the total study area was statistically significantly lower than the reference area, but that the prevalence in the 3-town area was not meaningfully different. However, the prevalence estimate in the 3-town area was slightly higher than that of the full study area. It is unclear whether the prevalence of MS is truly higher in these three communities, though: two different methods of cluster analysis were utilized to explore the possible role of the SWNAS in the occurrence of MS. Both methods found statistically significant clusters in the 3-community area near SWNAS. It seems likely that residential proximity to the base was not a factor because there was no trend of increasing MS cases closer to the base. Further, U.S. Census data suggests that in-migration rates for the 3 communities were substantially higher than elsewhere in Southeastern Massachusetts, thereby potentially increasing the prevalence estimates artificially.

As observed with the ALS estimate, the data suggest that the MS prevalence estimates for the total and 3-town areas may have been underestimated because a number of cases from secondary sources and from primary sources but whose medical records were incomplete or unavailable for review to verify diagnosis and so could not be included in the prevalence estimates. Applying the verification percentage found through the review of primary source cases, prevalence was higher for the total study area but still not higher than would be expected for the general population based upon prevalence values published in the scientific literature. Applying the same verification percentage to the numbers of cases for the 3-town area, the higher prevalence estimate appeared greater than what would be expected based on published figures.

6.3 Lessons Learned for Future ALS/MS Surveillance by Researchers

The ascertainment of possible cases from secondary sources served to evaluate the precision of prevalence estimates derived from primary sources only. In this study, some cases of ALS and MS were found to have possibly been missed by focusing only on ascertaining cases from the medical records of hospitals and private neurology practices. As a result, prevalence estimates were derived to assess possible underestimation of prevalence by including cases from primary and some secondary sources whose medical records were not available to verify diagnosis.

It was also found that up to 30% of MS cases and 56% of ALS cases could be misclassified as definite or probable cases if only ICD codes and statements of diagnosis in medical records are used and not verified diagnoses. It is unlikely that all cases reported would be verified with a definite or probable diagnosis because of the difficulties in diagnosing these diseases, many cases in this study did not have their diagnoses verified because of incomplete clinical information. Adequate clinical information should be collected so that the diagnosis of cases from all sources can be verified, including the identification of deceased cases that may not have been reported by a neurologist. In addition, some cases were classified as possible or suspected when adequate clinical data was available. Therefore, in addition to the collection of more complete clinical information for case verification, the re-review of the possible and suspected cases at some later date (e.g., 6-month intervals) might be necessary in order to capture disease progression that might not be reported by a provider who has already submitted the case. Otherwise, these progressed cases could be missing from surveillance statistics and bias surveillance findings.

The number of confirmed cases of definite and probable ALS and MS from death certificates was not clear from this study because medical records for these cases could not be reviewed. However, the data collected suggested that neurologists might have not always report cases that had died during the study period. Therefore, excluding cases from these and other secondary sources may have lead to an underestimation of prevalence.

Findings suggested that the ascertainment of some MS cases from primary sources might have been missed if they had not been diagnosed or treated within the surveillance area or had not been diagnosed or treated at an MS clinic or hospital in Boston.

All hospitals and neurologists believed to serve the residents of the 30-community study area that were identified agreed to participate in the surveillance effort except for a Veterans Administration hospital. This success was attributed to clear communication with providers regarding the public health authority consistent with HIPAA regulations to access health records and the understood need for the surveillance of these diseases in Massachusetts.

6.4 Environmental Exposures and ALS/MS

The numbers of ALS cases were too small to apply statistical cluster detection methods, but no cases were identified in Middleborough during the surveillance period, which was the focus of community concern because of possible exposure to hazardous waste sites. Statistical cluster detection methods were able to be applied to determine if the distribution of MS cases in the study area was clustered, with particular focus on the area surrounding the SWNAS where there was community concern about possible exposure to environmental contaminants. The analyses found that the prevalence of MS was greater near the base than elsewhere in the study area. However, because the number of cases did not appear to increase with decreasing distance to the base and because of possible effects of in-migration, the data do not suggest that environmental factors associated with the SWNAS played a primary role in the development of MS. Importantly, because no individual level information was obtained in this project, such as through personal interviews, it is not possible to conclude whether the higher prevalence in this area may be due to some other environmental factors or to risk factors not available for analysis (e.g., occupational exposures, residential history, and family medical histories).

6.5 Recommendations

1. MDPH is now conducting ALS surveillance statewide consistent with Section 26 of Chapter 140 of the Massachusetts Acts of 2003 and should summarize statewide and community surveillance estimates.
2. MDPH should provide copies of the ATSDR/MDPH Health Consultations on Gerson Properties and Middleborough Plating to local health, legislative representatives, and community residents upon completion.
3. MDPH/BEH is currently funded by the U.S. Centers for Disease Control and Prevention (CDC) Environmental Public Health Tracking branch to continue development of health and environmental electronic surveillance systems. As

part of that effort, MDPH should make community-level ALS data available to the public on the MDPH website.

4. MDPH should continue to monitor the occurrence of MS using available electronic systems, such as hospitalization data.

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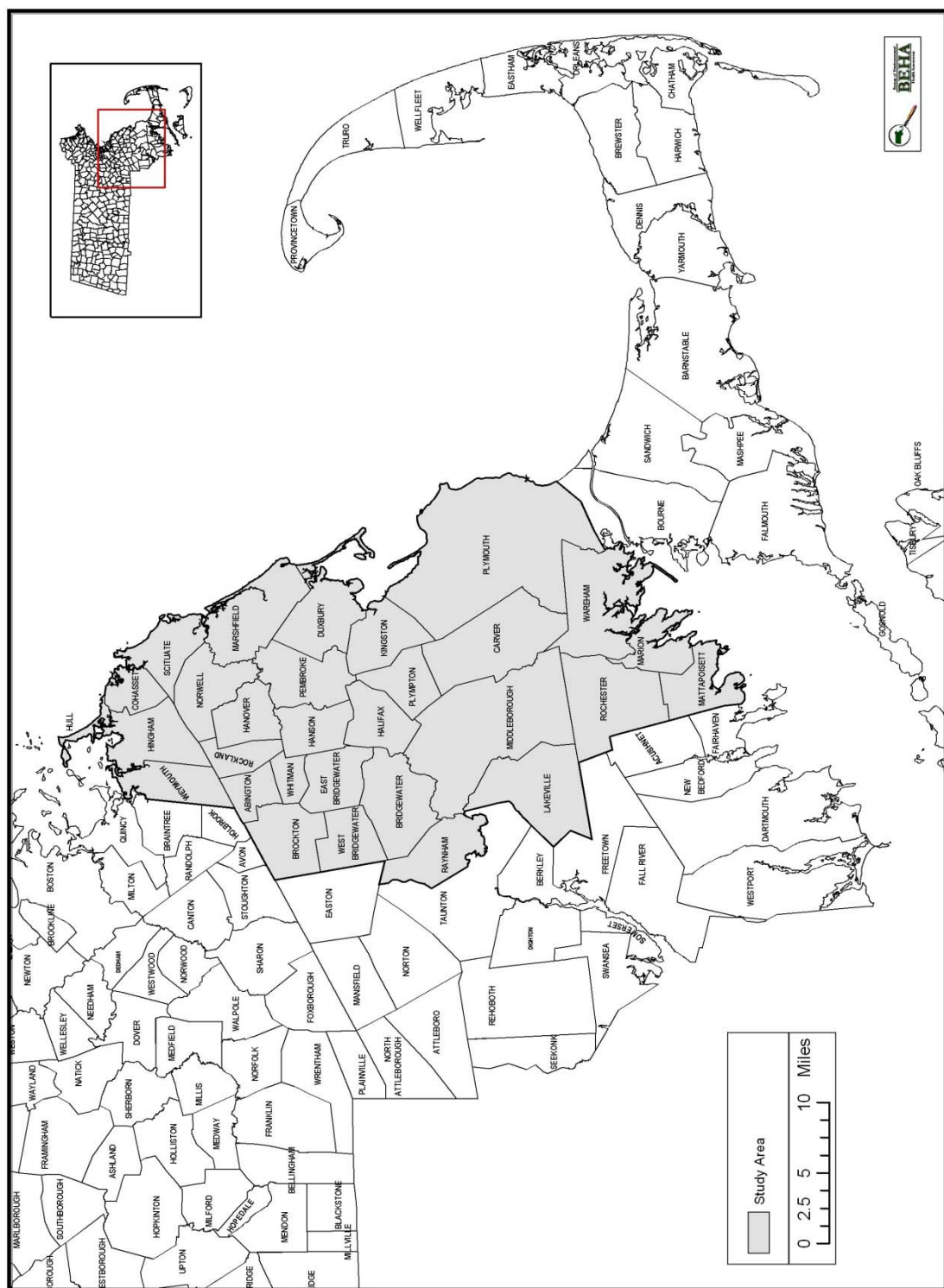
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Figures

Figure 1: Massachusetts communities in the total surveillance area



Data Source: MassGIS, 2002

Figure 2: Case Ascertainment for ALS

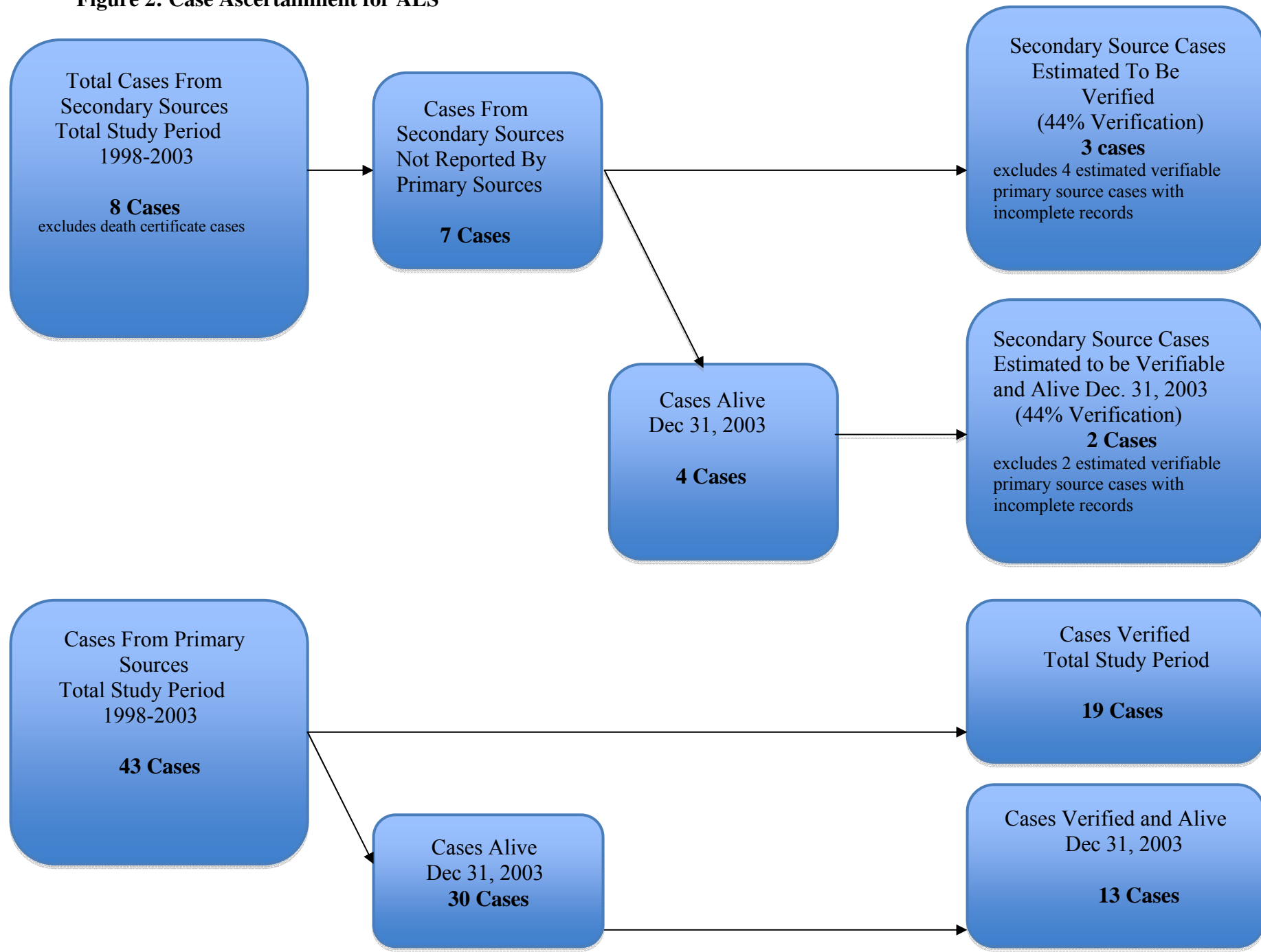


Figure 3: Case Ascertainment for MS

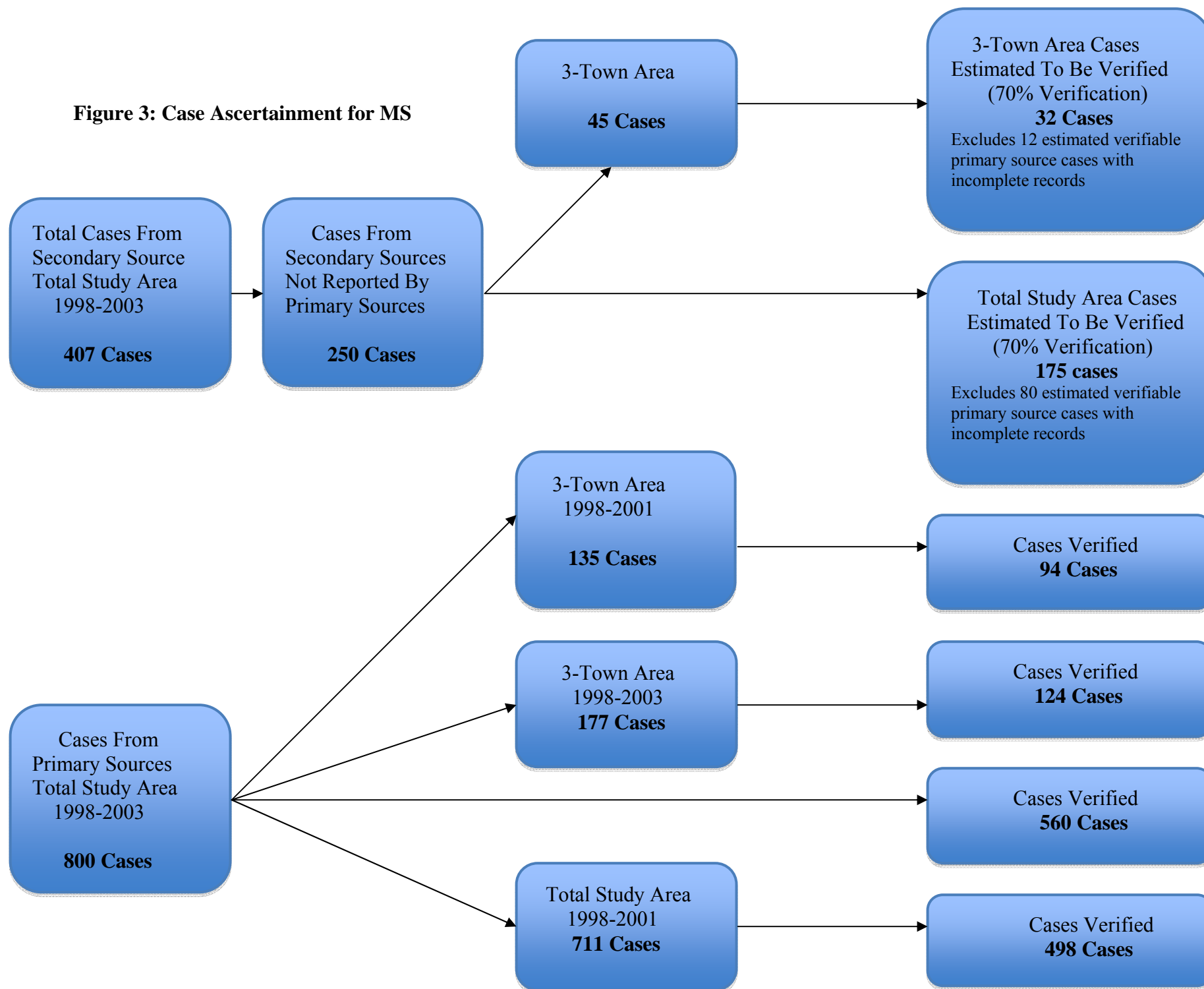


Figure 4: Data collection milestones

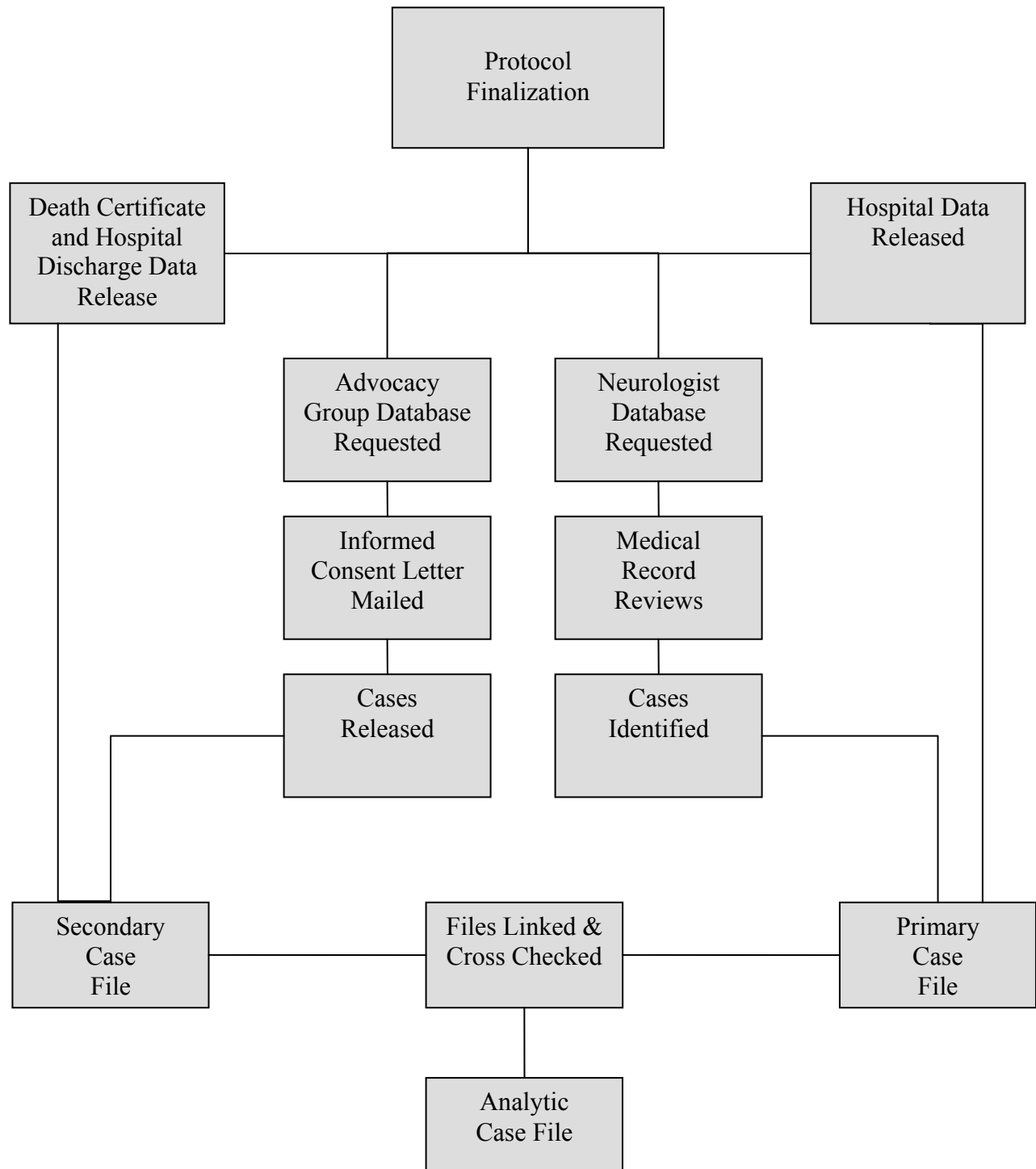


Figure 5: Prevalence of Multiple Sclerosis (MS) per 100,000 by census tract

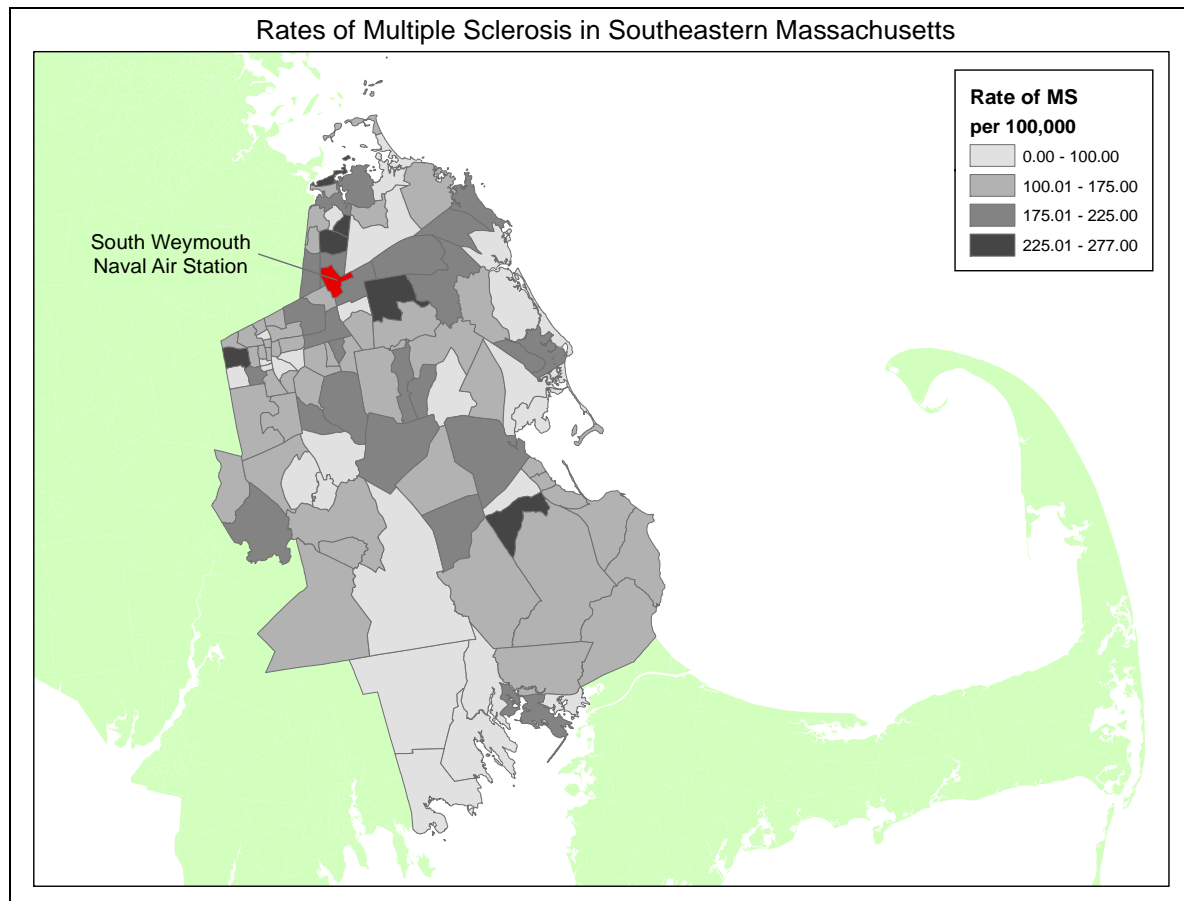


Figure 6: Multiple Sclerosis (MS) cluster location utilizing the spatial scan statistic and adjusting for gender

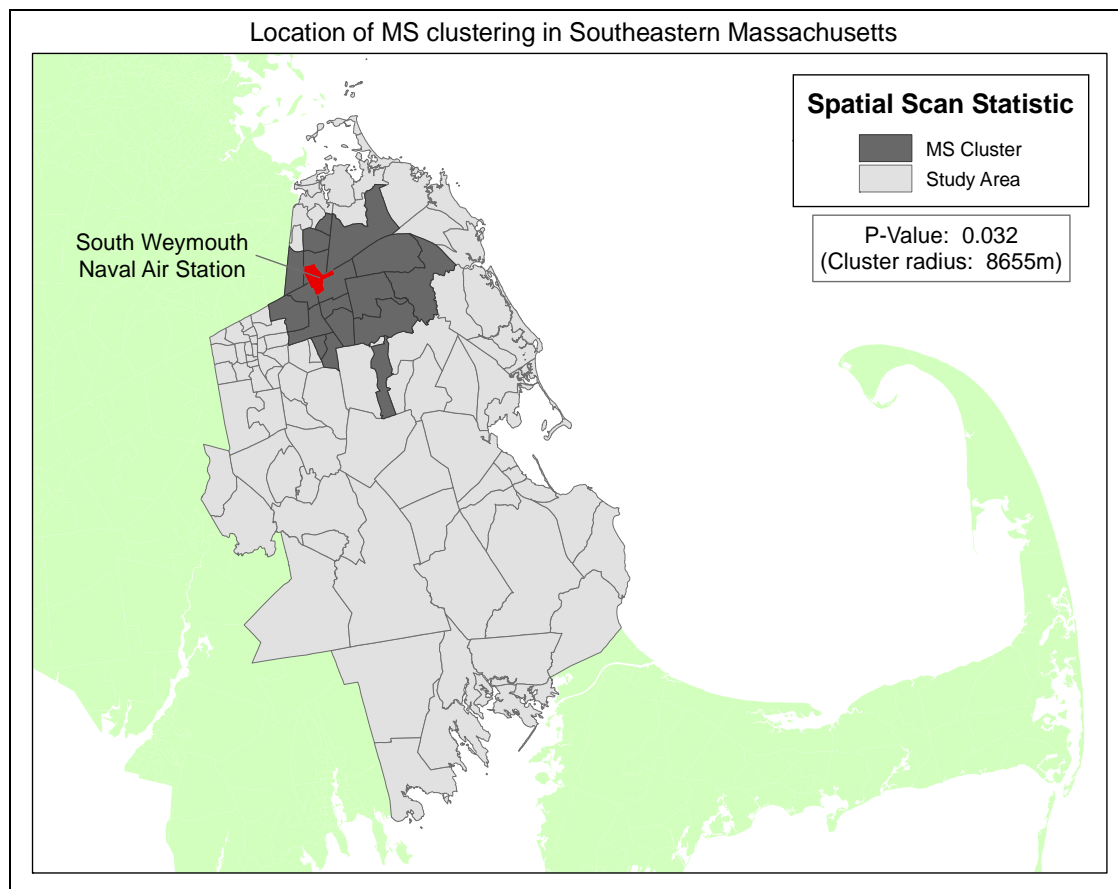
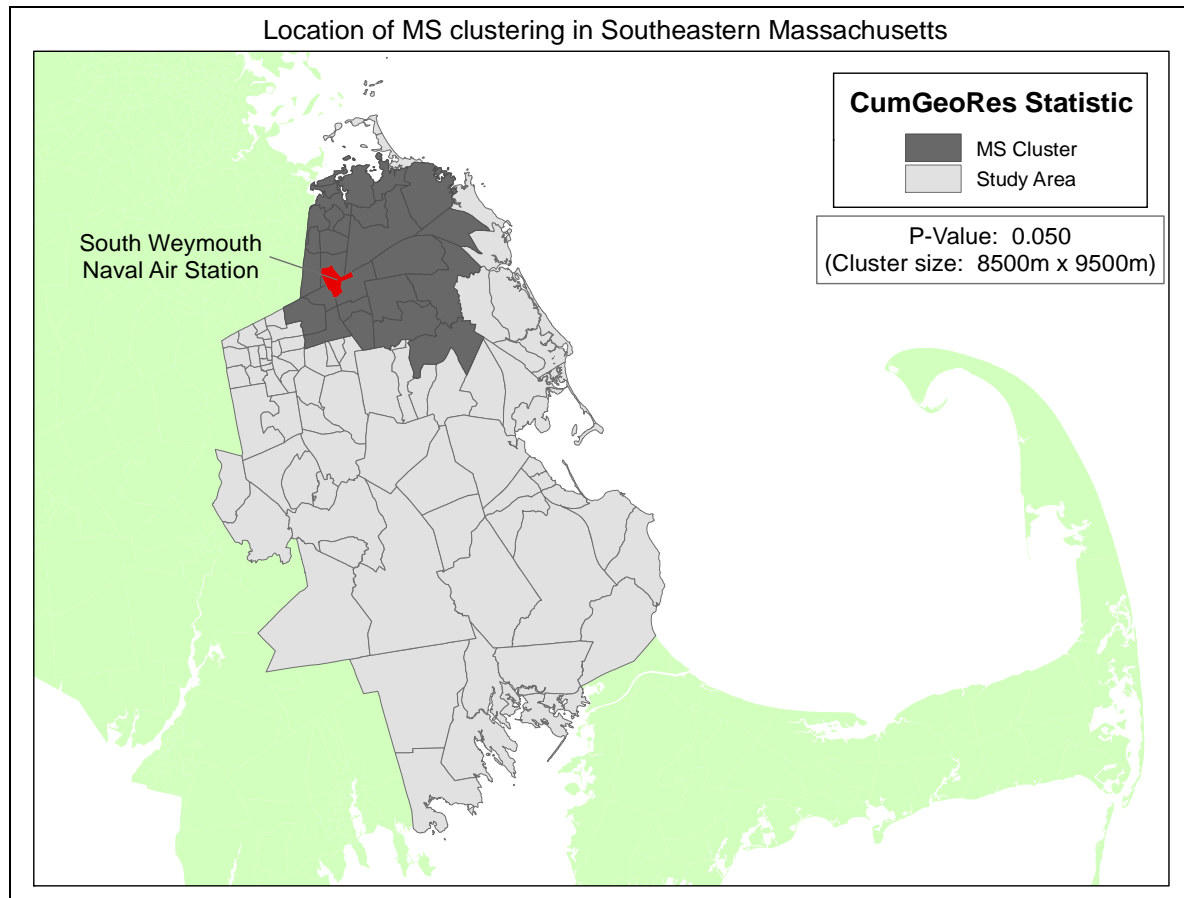


Figure 7: Multiple Sclerosis (MS) cluster location utilizing CumGeoRes and adjusting for gender



Tables

Table 1: General population characteristics for the surveillance area¹

Subject	Number
Total Population	545,810
GENDER	
Male	265,157
Female	280,653
Age	
<30	212,137
30-39	89,186
40-49	89,290
50-59	67,757
60-69	38,653
70+	48,787
Race	
Hispanic	12,405
Non-Hispanic White	483,238
Non-Hispanic Black	22,487
Other	27,680

¹US Census 2000 Summary File 1 (SF1) - Downloaded from: <http://factfinder.census.gov>

Table 2: Poser diagnostic criteria for Multiple Sclerosis (MS)

Category	Attacks	Clinical Evidence of Lesions	Paraclinical Evidence	Cerebrospinal Fluid OB/IgG
Clinically definite multiple sclerosis (CDMS)				
CDMS A1	2	2		
CDMS A2	2	1	And 1	
Laboratory-supported definite multiple sclerosis (LSDMS)				
LSDMS B1	2	1	Or 1	+
LSDMS B2	1	2		+
LSDMS B3	1	1	And 1	+
Clinically probable multiple sclerosis (CPMS)				
CPMS C1	2	1		
CPMS C2	1	2		
CPMS C3	1	1	And 1	
Laboratory-supported probable multiple sclerosis (LSPMS)				
LSPMS D1	2			+

Notes: CSF = cerebrospinal fluid

OB/IgG = oligoclonal bands or increased IgG synthesis

Table 3: McDonald diagnostic criteria for Multiple Sclerosis (MS)

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks: objective clinical evidence of 2 or more lesions	None
Two or more attacks: objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by magnetic resonance imaging (MRI) <i>or</i> Two or more MRI-detected lesions consistent with MS plus positive cerebrospinal fluid (CSF) <i>or</i> Await further clinical attack implicating a different site
One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI <i>or</i> 2 nd clinical attack
One attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI <i>or</i> Two or more MRI-detected lesions consistent with Multiple Sclerosis (MS) plus positive CSF <i>and</i> Dissemination in time, demonstrated by MRI <i>or</i> 2 nd clinical attack
Insidious neurological progression suggestive of MS	Positive CSF <i>and</i> Dissemination in space, demonstrated by 1) Nine or more T2 lesions in brain <i>or</i> 2) 2 or more lesions in spinal cord, <i>or</i> 3) 4-8 brain plus 1 spinal cord lesion <i>or</i> abnormal VEP associated with 4-8 brain lesions, or with fewer than 4 brain lesions plus 1 spinal cord lesion demonstrated by MRI <i>and</i> Dissemination in time, demonstrated by MRI <i>or</i> Continued progression for 1 year

Table 4: ICD Codes for Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS)

Multiple Sclerosis	ALS
ICD-9-CM Codes	
340 MS	335.2 Motor neuron disease
337.3 (including 337.30, 337.31, and 337.32) Optic neuritis	335.20 ALS
323.1 Other cerebellar ataxia	335.21 Progressive muscular atrophy
323.9 Unspecified cause of encephalitis	335.22 Progressive bulbar palsy
334.9 Spinocerebellar disease, unspecified	
336.9 Unspecified disease of spinal cord, includes myelopathy, not otherwise specified (NOS)	
341.8 Other demyelinating diseases of central nervous system	
341.9 Demyelinating disease of central nervous system, unspecified	
344 Other paralytic syndromes	
357.81 Chronic inflammatory demyelinating polyneuritis	
ICD-10 Codes	
G35 MS	G12.2 Includes motor neuron disease
G04 Encephalitis, myelitis, and encephalomyelitis	Familial motor neuron disease
G11 Hereditary ataxia	Lateral sclerosis: <ul style="list-style-type: none"> • Amyotrophic • Primary
G36 Other acute disseminated demyelination	Progressive: <ul style="list-style-type: none"> • Bulbar palsy • Spinal muscular atrophy
G37 Other demyelinating diseases of central nervous system	
G83 Other paralytic syndromes	
H46 Optic neuritis	
H48.1 Retrobulbar neuritis in diseases classified elsewhere	

Table 5: Primary sources of Amyotrophic Lateral Sclerosis (ALS) cases, Total Study Area, 1998-2003*

				Total # of Cases	Percent of Total
<i>Single Source</i>				39	(90.7%)
	Hospital medical records	36	(92.3%)		
	Outpatient clinics, Health Maintenance Organizations (HMOs), and private neurologists	3	(7.7%)		
<i>2 Sources</i>				4	(9.3%)
	2 hospitals	0			
	Hospital + private neurologist	4	(100%)		
	Hospital + HMO	0			
	2 private neurologists	0			
	Private neurologist + HMO	0			
<i>3+ Sources</i>				0	(0.0%)
TOTAL:				43	(100%)

*Cases with a clear statement of diagnosis in the medical records.

Table 6: Descriptive characteristics of Amyotrophic Lateral Sclerosis (ALS) cases, Total Study Area, 1998-2003

	ALS Cases for 1998- 2003 period¹ (%)	Population
Total	43 (100)	545,810
Female	24 (53.5)	280,653
Male	19 (46.5)	265,157
<30	0 (0.0)	212,137
30-39	4 (9.3)	89,186
40-49	3 (7.0)	89,290
50-59	11 (25.6)	67,757
60-69	7 (16.3)	38,653
70+	18 (41.9)	48,787
Unknown	0 (0.0)	0
Hispanic	0 (0.0)	12,405
Non-Hispanic White	9 (20.9)	483,238
Non-Hispanic Black	0 (0.0)	22,487
Other/Unknown	34 (79.1)	2, 680

¹ Cases are those prior to verification of diagnosis.

Table 7: Amyotrophic Lateral Sclerosis (ALS) cases identified from secondary data sources, 1998-2003

Data Source	Total Number Identified	Number Identified from Primary Data Sources (%)	Number Identified only from the Secondary Source (%)
ALS			
West Roxbury Veterans Administration Hospital	not reported	-	-
Rhode Island Naval Hospital	2	1 (50%)	1 (50%)
ALS Association	4	0	4 (100%)
ALS Family Charitable Foundation	2	0	2 (100%)
Death Certificates	58	13 (22%)	45 (78%)

Table 8: Results of the verification of diagnosis through neurologist-reviewed Amyotrophic Lateral Sclerosis (ALS) medical records, Total Study Area, 1998-2003*

Record review result	Number of reviewed records		
	Females (%)	Males (%)	Total (%)
Record Abstraction			
Definite	15 (62.5)	14 (73.7)	29 (67.4)
Probable	9 (37.5)	5 (26.3)	14 (32.6)
Total	24 (100)	19 (100)	43 (100)
Neurologist applied El Escorial criteria ¹			
Definite	4 (16.7)	3 (15.8)	7 (16.3)
Probable	8 (33.3)	4 (21.1)	12 (27.9)
Possible/Suspected	6 (25.0)	6 (31.6)	12 (27.9)
Not ALS	0	3 (15.8)	3 (7.0)
Indeterminate	6 (25.0)	3 (27.5)	9 (20.9)
Total	24 (100)	19 (100)	43 (100)
Verification of definite or probable diagnosis	19/43 (44.2%)		
Cases not verified	24/43 (55.8%)		

* Results are based upon the review of all records from primary sources.

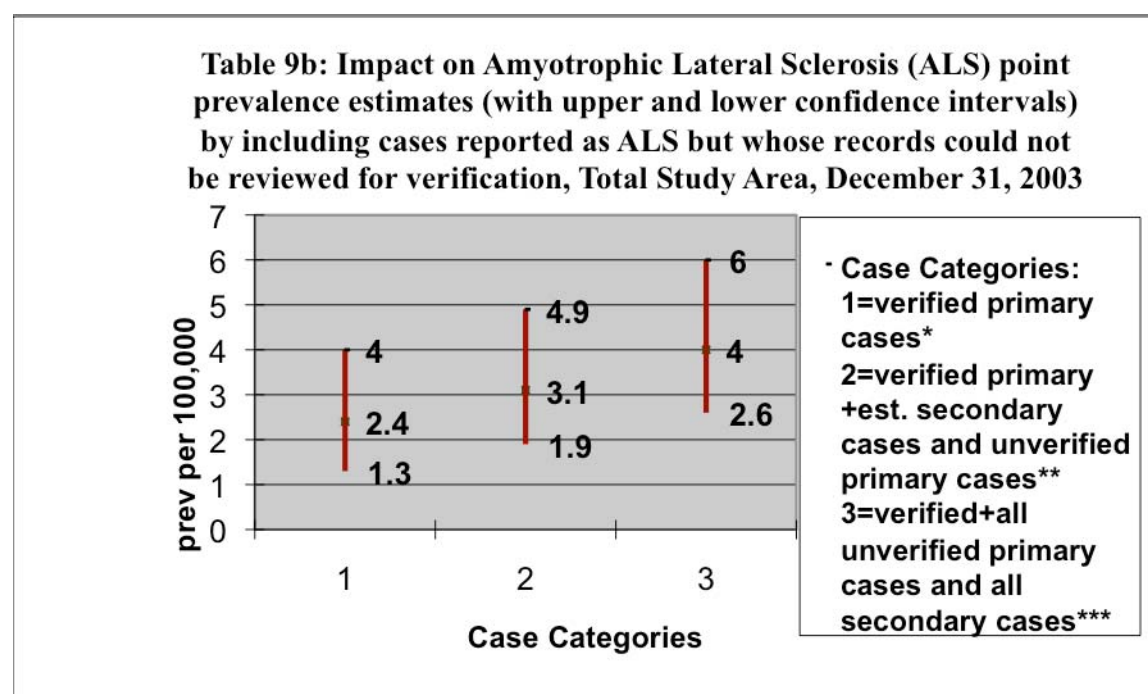
¹ Brook BR. 1994. El Escorial World Federation of Neurology criteria. Journal of the Neurological Sciences 124 Supplement: 96-107.

Table 9a: Geographic comparisons of Amyotrophic Lateral Sclerosis (ALS) point prevalence, Total Study Area to the Reference Area, December 31, 2003¹

Geographic Area	Cases	Population (2000 Census)	Point Prevalence per 100,000 (95% CI)	Crude Prevalence Ratio (95% CI)
Reference Area¹	8	203,783	3.9 (2.0-7.7)	-
Study Area - Verified Primary Source Cases Only²	13	545,810	2.4 (1.3-4.0)	0.61 (0.25-1.46)

¹Source of Reference Area prevalence: Turabelidze, G. et al. An epidemiologic investigation of amyotrophic lateral sclerosis in Jefferson County, Missouri, 1998-2002. NeuroToxicology 29:81-86. 2008a.

²Analysis based on cases with definite or probable diagnosis following verification, alive December 31, 2003.



* Category 1 = all verified cases from primary sources only, alive December 31, 2003.

** Category 2 = all verified cases from primary sources plus 44.2% of cases reported from advocacy groups and from primary sources with insufficient records for review (including RI Naval Hospital), alive December 31, 2003.

***Category 3 = All verified cases from primary sources plus all cases from primary sources with insufficient records for review + all cases from advocacy groups, alive December 31, 2003.

Table 10: Primary sources of Multiple Sclerosis (MS) cases, Total Study Area, 1998-2003*

		#	(%)	Total # of Cases	Percent of Total
<i>Single Source</i>				600	(75%)
	Hospital medical records	401	(67%)		
	Outpatient clinics, Health Maintenance Organizations (HMO)s, and private neurologists	199	(33%)		
<i>2 Sources</i>				167	(21%)
	2 hospitals	96	(57%)		
	Hospital + private neurologist	46	(28%)		
	Hospital + HMO	18	(11%)		
	2 private neurologists	5	(3%)		
	Private neurologist + HMO	2	(1%)		
<i>3+ Sources</i>				33	(4%)
TOTAL:				800	(100%)

*Cases where medical records included a clear statement of diagnosis.

Table 11: Descriptive characteristics of Multiple Sclerosis (MS) cases, Total Study Area, 1998-2003

	MS cases¹ (%)	Population
Total	800 (100)	545,810
Sex		
Female	603 (75.4)	280,653
Male	197 (24.6)	265,157
Age		
< 30	57 (7.1)	212,137
30-39	167 (20.9)	89,186
40-49	230 (28.8)	89,290
50-59	211 (26.4)	67,757
60-69	96 (12.0)	38,653
70 +	34 (4.3)	48,787
unknown	5 (0.6)	-
Race/ethnicity		
Hispanic	1 (0.1)	12,405
Non-Hispanic White	230 (28.8)	483,238
Non-Hispanic Black	0 (0.0)	22,487
Other/Unknown	569 (71.1)	27,680

¹ Cases include all those reported from primary sources.

Table 12: Multiple Sclerosis (MS) cases identified from secondary data sources, 1998-2003

Data Source	Total Number Identified	Number Identified from Primary Data Sources (%)	Number Identified only from the Secondary Source (%)
MS			
West Roxbury Veterans Administration Hospital	not reported	-	-
Rhode Island Naval Hospital	42	5 (12%)	37 (88%)
Massachusetts Department of Public Health Patient Advocacy Program	26	26 (100%)	0
MS Society	204	85 (42%)	119 (58%)
Death Certificates	58	6 (10%)	52 (90%)
Community Advocacy Group (AWARES)	77	35 (45%)	42 (55%)

Table 13: Outcome of reviewed medical records according to Multiple Sclerosis (MS) diagnostic criteria, Total Study Area, 1998-2003*

Neurologist record review results	Number of reviewed records					
	Females (%)		Males (%)		Total (%)	
Neurologist applied Poser criteria ¹						
Definite	46	(69.7)	13	(54.2)	59	(65.6)
Probable	8	(12.1)	5	(20.8)	13	(14.4)
Possible	0	(0.0)	0	(0.0)	0	(0.0)
Not MS	5	(7.6)	0	(0.0)	5	(5.1)
Indeterminate	7	(10.6)	6	(25.0)	13	(14.4)
Total	66	(100)	24	(100)	90	(100)
Neurologist applied McDonald criteria ²						
Definite	47	(71.2)	17	(70.8)	64	(71.1)
Possible	4	(6.1)	4	(16.7)	8	(8.9)
Presumptive	0	(0.0)	0	(0.0)	0	(0.0)
Not MS	4	(6.1)	0	(0.0)	4	(4.4)
Indeterminate	11	(16.7)	3	(12.5)	14	(15.6)
Total	66	(100)	24	(100)	90	(100)

* Results are based upon the review of a sample of records.

¹ Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13:227-231.

² McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001; 50:121-7.

Table 14: Results of verification of diagnosis through neurologist-reviewed Multiple Sclerosis (MS) medical records and agreement between Poser and McDonald diagnostic criteria, Total Study Area, 1998-2003

		McDonald				
		Definite	Possible	Inconclusive	Not MS	Total
Poser	Definite	59	0	0	0	59
	Probable	4	6	3	0	13
	Indeterminate	1	1	11	0	13
	Not MS	0	1	0	4	5
	Total	64	8	14	4	90
Agreement ¹						
Definite or Probable		63 (70.0%)				
Not MS or Indeterminate		15 (16.7%)				
Disagreement ¹						
Definite-Probable/ Possible		6 (6.7%)				
Definite-Probable/ Not MS- Indeterminate		3 (3.3%)				
Other		3 (3.3%)				

¹Diagnostic agreement and disagreement was for the Poser versus McDonald criteria.

Table 15a: Geographic comparisons of Multiple Sclerosis (MS) prevalence, Total Study Area to the Reference Area¹, 1998-2001

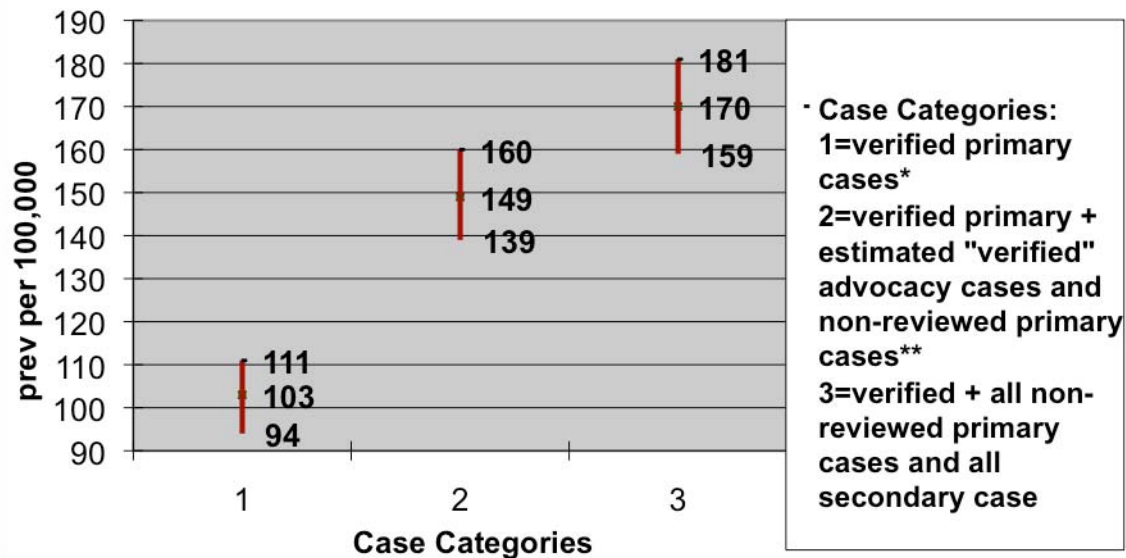
Geographic Area	Cases	Population	Period Prevalence per 100,000 for 1998-2001 (95% CI)	Crude Prevalence Ratio (95% CI)
Reference Area¹	139	120,799	115 (97-135)	-
Study Area - Verified Primary Source Cases Only²	498	545,810	91 (84-100)	0.79 (0.66-0.95)*

* Indicates prevalence is statistically significantly lower.

¹Source of Reference Prevalence: Neuberger, JS, et al. Prevalence of multiple sclerosis in a residential area bordering an oil refinery. Neurology 63: 1796-1802. 2004.

²Analysis based on cases with definite or probable diagnosis assuming a 70% diagnosis verification percentage by both the Poser and McDonald criteria (number of cases adjusted for the number of expected verified cases based upon the study's verification from Table 14), identified during the period 1998-2003.

Table 15b: Impact on Multiple Sclerosis (MS) period prevalence estimates (with upper and lower confidence intervals) by including cases reported as MS but whose records could not be reviewed for verification, Total Study Area, 1998-2003



*Category 1 = all verified cases from primary sources identified during the period 1998-2003.

**Category 2 = all verified cases from primary sources plus 70% of cases reported during 1998-2003 from advocacy groups, death certificates, and primary sources with insufficient records for review (including cases from the Naval Hospital). The 70% represents the percent of cases from primary sources that were verified (refer to Table 14).

***Category 3 = all verified cases from primary sources plus 70% of all cases from primary sources with insufficient records for review and all cases from secondary sources identified during the period 1998-2003.

Table 16a: Geographic Comparisons of Multiple Sclerosis (MS) Period Prevalence, Weymouth/Abington/Rockland Study Area to the Reference Area and Total Study Area, 1998-2001¹

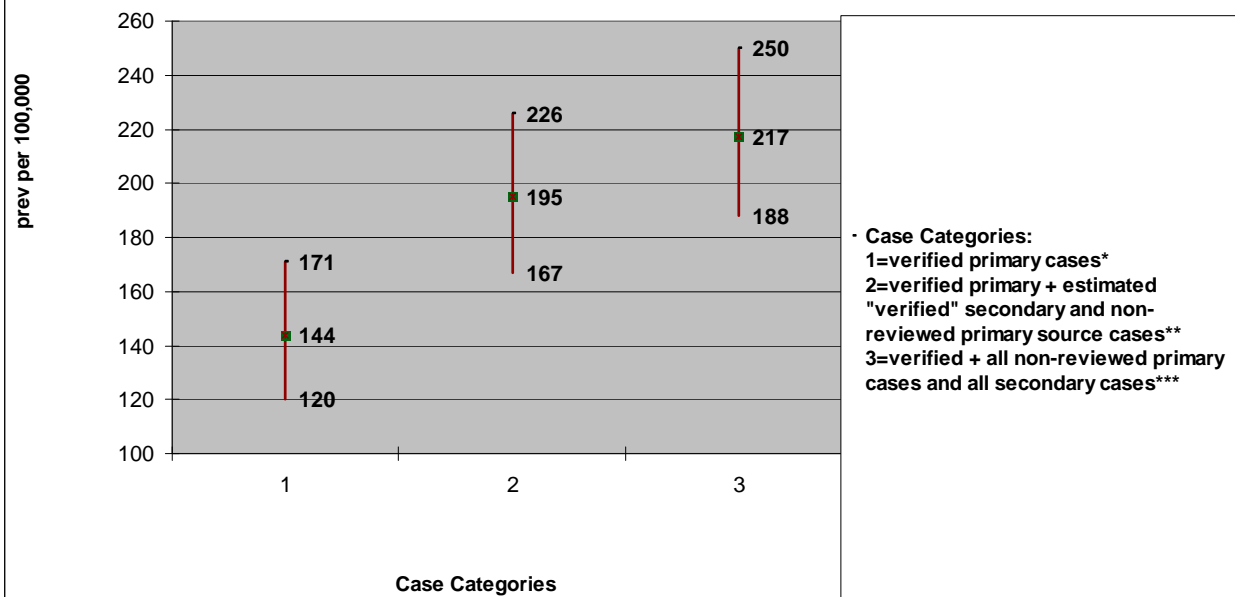
Geographic Area	Cases	Population	Period Prevalence per 100,000 for 1998-2001 (95% CI)	Crude Prevalence Ratio (95% CI)
Reference Area ¹	139	120,799	115 (97-135)	-
Verified Primary Source Cases for Total Study Area ²	498	545,810	91 (84-100)	
Verified Primary Source Cases Only - 3 Town Area ³	94	86,108	109 (89-133)	
Comparison with Reference Area ¹				0.95 (0.73-1.23)
Comparison with Total Study Area ²				1.20 (0.96-1.49)

¹Source of Reference Prevalence: Neuberger, JS, et al. Prevalence of multiple sclerosis in a residential area bordering an oil refinery. Neurology 63: 1796-1802. 2004.

²Analysis based on cases with definite or probable diagnosis assuming a 70% diagnosis verification rate by both the Poser and McDonald criteria (number of cases adjusted for the number of expected verified cases based upon the study's verification rate from Table 14), identified during the period 1998-2003.

³Analysis based on cases with definite or probable diagnosis assuming a 70% diagnosis verification rate by both the Poser and McDonald criteria (number of cases adjusted for the number of expected verified cases based upon the study's verification rate from Table 14), identified during the period 1998-2003 among residents of Weymouth, Abington, and Rockland.

Table 16b: Impact on Multiple Sclerosis (MS) period prevalence estimates (with upper and lower confidence intervals) by including cases reported as MS but whose records could not be reviewed for verification, 3-Town Study Area, 1998-2003



*Category 1 = all verified cases from primary sources.

**Category 2 = all verified cases from primary sources plus 70% of cases reported from advocacy groups, death certificates, and primary sources with insufficient records for review (including cases from the RI Naval Hospital). The 70% represents the percent of cases from primary sources that were verified (refer to Table 14).

***Category 3 = All verified cases from primary sources plus all cases from primary sources with insufficient records for review and all cases from advocacy groups

Appendices

Appendix 1: Health Care Provider Letter



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

MITT ROMNEY
GOVERNOR

KERRY HEALEY
LIEUTENANT GOVERNOR

RONALD PRESTON
SECRETARY

CHRISTINE C. FERGUSON
COMMISSIONER

Date

Health Care Provider Name
Address

Dear (Provider's Name):

The Massachusetts Department of Public Health's (MDPH) Bureau of Environmental Health Assessment (BEHA) is conducting epidemiological surveillance to estimate the prevalence of Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) in 30 communities in Southeastern Massachusetts. We have been awarded federal monies for this project from the Agency for Toxic Substances and Disease Registry (ATSDR), and are requesting your participation in this important investigation.

We will be asking your cooperation by identifying your patients with MS or ALS with an address in our surveillance area. Attached is a list of the ICD codes for these diseases (and related conditions), to assist you if you will be conducting a computerized search using ICD codes. The surveillance area includes 30 communities in southeastern Massachusetts. Also attached is a list of these communities with their zip codes. Subsequent to identifying individuals with these diseases, we will request access to their medical records to abstract certain personal and diagnostic information. The original records will not leave your office or medical facility, and we will make every effort to be unobtrusive when abstracting information from the records.

Based on the fact that this project involves public health surveillance activities as authorized by state regulations and does not constitute research involving human subjects, the Human Research Review Committee of the MDPH has waived the need for its review. The MDPH regulatory authority to access health records for the purpose of conducting public health surveillance is granted through regulations cited in 105 CMR 300.192. Under these regulations, the MDPH is authorized to collect from health care providers data on individuals evaluated for or diagnosed with ALS or MS (as well as other diseases). This regulatory authority also allows covered entities under the Health Insurance and Portability Act (HIPAA) to disclose protected health information to the MDPH without obtaining written authorization of the data subject. The HIPAA privacy regulations specifically permit such disclosures of protected health information

to a public health authority that is authorized by law to receive such information (see 45 CFR 164.512 (b)).

It is the policy of the MDPH to ensure that all public health investigations, including surveillance, be conducted in a manner that protects the rights and privacy of individuals to the greatest extent feasible and that the investigations comply with all applicable state and federal requirements. Also, it is important for you to know that, under Massachusetts General Laws Chapter 111, Section 24A, all information collected by the MDPH as part of this surveillance, is strictly confidential and is not admissible as evidence in any legal proceeding. Furthermore, the statute states that anyone providing information to the MDPH as part of this surveillance shall not be liable for any damages related to disclosure.

We will call you soon to set up a time for our visit. If you have any questions, please contact Jan Sullivan (Project Coordinator) at 617 624-5757. We look forward to working with you and making a contribution to our understanding of MS and ALS in the Commonwealth.

Sincerely,

Suzanne Condon
Co-Principal Investigator
Assistant Commissioner

Robert Knorr, Ph.D.
Co-Principal Investigator
Deputy Director

Surveillance Area Communities

<i>Surveillance Area Communities</i>	<i>Zip Codes</i>
Abington	02351
Bridgewater	02324, 02325
Brockton	02301, 02302, 02303, 02304, 02305
Carver	02330, 02355, 02366
Cohasset	02025
Duxbury	02332, 02331
East Bridgewater	02324, 02333, 02337
Halifax	02338
Hanover	02339, 02340
Hanson	02341, 02350
Hingham	02343, 02344, 02018
Hull	02045
Kingston	02364
Lakeville	02347
Marion	02738
Marshfield	02050, 02065, 02020, 02041, 02047, 02051, 02059
Mattapoisett	02739
Middleborough	02344, 02348, 02349, 02346
Norwell	02061, 02018
Pembroke	02359, 02327, 02358
Plymouth	02360, 02361, 02362, 02345, 02381
Plympton	02367
Raynham	02767
Rochester	02770
Rockland	02370
Scituate	02066, 02040, 02055, 02060
Wareham	02571
West Bridgewater	02379
Weymouth	02188, 02189, 02190, 02191
Whitman	02382

ICD Codes for MS and ALS

<i>Multiple Sclerosis</i>	<i>ALS</i>
340 MS	335.2 Motor neuron disease
337.3 (including 337.30, 337.31, and 337.32) Optic neuritis	335.20 ALS
323.1 Other cerebellar ataxia	335.21 Progressive muscular atrophy
323.9 Unspecified cause of encephalitis	335.22 Progressive bulbar palsy
334.9 Spinocerebellar disease, unspecified	
336.9 Unspecified disease of spinal cord, includes myelopathy NOS	
341.8 Other demyelinating diseases of central nervous system	
341.9 Demyelinating disease of central nervous system, unspecified	
344 Other paralytic syndromes	
357.81 Chronic inflammatory demyelinating polyneuritis	

Appendix 2: Medical Record Abstracting Short Form

Medical Record Abstracting Short Form

Hospital/office containing record: _____

Hospital/office address: _____

Is this record from a hospital? ____ Yes ____ No

Doctor's Name: _____

Does this facility/clinic maintain electronic records? ____ Yes ____ No

Medical Record Number: _____

Question 1: Did the patient live in the surveillance area between 1998 and 2003?

____ Yes ____ No

If yes or you have good reason to think yes (even though there is some uncertainty from the record), indicate your level of confidence that the patient lived in the surveillance area between 1998 and 2003:

____ Reasonably confident ____ Somewhat confident ____ Unsure

Question 2: Did the patient visit the neurologist in one of the following calendar years: 1998, 1999, 2000, 2001, 2002, or 2003?

____ Yes ____ No

Question 3: Based upon the physician's impression does the patient have the disease?

____ definite ____ probable ____ unsure ____ not ALS

Record the year of diagnosis: _____

Indicate your level of confidence in the year of diagnosis:

____ reasonably confident
____ somewhat confident
____ unsure

Is record review needed at another office/clinic? ____ Yes ____ No

If record review is needed at another office/clinic, please indicate name and address:

****If the answer to question 1 is yes and you are reasonably confident or somewhat confident about your answer, if the answer to question 2 is yes, and if the answer to question 3 is definite or probable or unsure, then continue filling out this form. If no, stop.**

Assign case ID number: _____

Patient's Name: _____

Date of Birth: _____ (M/D/Y)

Gender: _____ M _____ F

Race Ethnicity:

_____ Hispanic
_____ Non-Hispanic White
_____ Non-Hispanic Black
_____ Other/Unknown

Is there a family history of ALS? ____ Yes ____ No ____ Unsure

If yes, what relative? _____

Veteran Status:

_____ Yes
_____ No
_____ Unknown

If yes, what branch of service:

_____ Army	_____ Marines
_____ Navy	_____ National Guard
_____ Air Force	

Did patient fight in a war?

_____ No
_____ Yes

What war?

_____ World War II
_____ Korean
_____ Vietnam
_____ Gulf War
_____ Other

Occupation: _____ Usual _____ Most recent _____ Unknown _____

Patient's Residence during the Surveillance Period:

Street: _____

City: _____ State: _____ Zip: _____

Patient's Residence at the Time of Diagnosis:

Street: _____

City: _____ State: _____ Zip: _____

Is the patient deceased? ____ Yes ____ No ____ Unsure

If yes, indicate date of death: _____ (year or exact date)

Case-Finding Sources. Check one:

- | | | |
|---|--|--|
| <input type="checkbox"/> Private Neurology Office | <input type="checkbox"/> Hospital Clinic | <input type="checkbox"/> Community Citizen Group |
| <input type="checkbox"/> MDPH MS Program | <input type="checkbox"/> Death certificate | <input type="checkbox"/> Hospital discharge data |
| <input type="checkbox"/> Patient Self Referral | <input type="checkbox"/> Advocacy Group | <input type="checkbox"/> Medical Record Department |

Abstractor's Name: _____

Date of Abstraction: _____

Appendix 3: Medical Record Abstracting Long Form

Multiple Sclerosis

Medical Record Abstracting Long Form

Demographic Information

Medical Record Number

Case Number

Name:

Address:

Street: _____

City: _____

State: _____ Zip code: _____

Medical History

Date of Diagnosis:

Date of Onset:

Family History of MS:

____ Yes ____ No ____
Unknown

Relative:

Initial Diagnosing Neurologist (if other than private or hospital neurologist):

Name: _____

Address: _____

Phone Number: _____

Attack History

(Note attack history using the spaces provided: otherwise, type in the patient's history.)

First Attack:

Date: _____

Area of the body affected by the attack: _____

Signs/symptoms:

Second Attack:

Date: _____

Area of the body affected by the attack: _____

Signs/symptoms:

Third Attack:

Date: _____

Area of the body affected by the attack: _____

Signs/symptoms:

Additional Comments

CSF Laboratory Testing

Oligoclonal Bands in CSF: ___Present ___Not Present

Oligoclonal Bands in Serum: ___Present ___Not Present

IgG Index: ___Normal ___Elevated

Protein: ___Normal ___Elevated

IgG Synthesis: ___Normal ___Elevated

Myelin Basic Protein: ___Normal ___Elevated

White Blood Cell Count: ___Normal ___Elevated

Comments:

MRI Testing

Photocopy MRI report(s). Summarize MRI findings below.

MRI Findings:

Evoked Potentials

Visual: ___Normal ___Abnormal

Brainstem Auditory: ___Normal ___Abnormal

Somatosensory: ___Normal ___Abnormal

Abstractor Information

Abstractor Name: _____

Abstractor Signature: _____

Date: _____

Abstractor Comments:

Remainder Of Form To Be Completed By Consulting Neurologist

MS Diagnosis:

Poser Criteria: ___ Definite MS ___ Probable MS

Comments:

McDonald Criteria: ___ Definite MS ___ Possible MS

Comments:

Neurologist Name: _____

Neurologist Signature: _____

Date: _____

Amyotrophic Lateral Sclerosis

Medical Record Abstracting Long Form

Medical History

Year of Onset:

Indicate your level of confidence
in the year of onset:

- ☐ reasonably confident
☐ somewhat confident
☐ unsure

Initial Diagnosing Physician/Neurologist:

Name: _____

Address: _____

Phone Number: _____

Clinical History

Please put a **check mark and a date** inside the box to indicate signs of lower and/or upper motor neuron degeneration

	<i>CNS Regions</i>			
Lower motor neuron signs	Bulbar Jaw, face, palate, tongue, larynx	Cervical Neck, arm, hand, diaphragm	Thoracic Back, abdomen	Lumbosacral Back, abdomen, leg, foot
Weakness				
Atrophy				
Fasciculations				

Upper motor neuron signs	Bulbar	Cervical	Thoracic	Lumbosacral
Spasticity				
Increased or clonic tendon reflexes (DTR's)				
Pseudobulbar features "Jaw-jerk"				
Hoffman reflex "Finger jerk"				
Extensor plantar response (Babinski)				
Sensory Symptoms				

Comments:

Electrophysiology Testing

Nerve Conduction Test:

Was a nerve conduction test performed?

- ☐ Yes
- ☐ No
- ☐ Unsure

If yes, characterize the results:

- ☐ Normal
- ☐ Abnormal
- ☐ Unsure

Date: _____

Location: _____

Results and Impression:

EMG:

Was a full EMG performed?

- ☐ Yes
- ☐ No
- ☐ Unsure

Note: If a full EMG was performed, then you only need to abstract the findings for the full EMG.

EMG 1:

Date: _____
Location: _____

Fibrillation potentials (activation/recruitment): ___ Normal ___ Abnormal
If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Large motor unit action potentials (amplitude): ___ Normal ___ Abnormal
If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Reduced recruitment: ___ Normal ___ Reduced ___ Slightly Reduced ___ Mildly Reduced
If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Overall Summary:

EMG 2:

Date: _____
Location: _____

Fibrillation potentials (activation/recruitment): ___ Normal ___ Abnormal
If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Large motor unit action potentials (amplitude): ___ Normal ___ Abnormal
If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Reduced recruitment: ___ Normal ___ Reduced ___ Slightly Reduced ___ Mildly Reduced
If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Overall Summary:

EMG 3:

Date: _____

Location: _____

Fibrillation potentials (activation/recruitment): ___ Normal ___ Abnormal

If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Large motor unit action potentials (amplitude): ___ Normal ___ Abnormal

If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Reduced recruitment: ___ Normal ___ Reduced ___ Slightly Reduced ___ Mildly Reduced

If abnormal, where: ___ upper extremity ___ lower extremity ___ bulbar ___ paraspinals

Overall Summary:

Neuroimaging studies

Were neuroimaging studies performed?

___ Yes

___ No

___ Unsure

Characterize the test results:

___ Normal

___ Abnormal

___ Unsure

X-rays:

Comment: _____

MRIs

Were MRIs performed?

☐ Yes

☐ No

☐ Unsure

Characterize the test results:

☐ Normal

☐ Abnormal

☐ Unsure

Summarize MRI findings below. Indicate region as head, neck, thoracic, or lumbosacral. If multiple MRIs, summarize each one separately.

Myelography

Were myelography studies *performed*?

☐ Yes

☐ No

☐ Unsure

Characterize the test results:

☐ Normal

___ Abnormal
___ Unsure

Myelography Comments:

Clinical Laboratory Tests:

Note: If the result is abnormal, report the value and the range of normal values in the comment section.

CSF: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Other lab tests:

Hematocrit: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

WBC: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

B-12: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Folate: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Lead: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Immunoelectrophoresis (IEP): ___ Normal ___ Abnormal ___ Unsure
___ Not done

Date: _____

Comments: _____

Sedimentation rate (ESR): ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Lyme: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Thyroid: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

GM1 (anti-GM antibodies): ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Electrolytes: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Glucose: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

CPK (creatinine kinase): ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Bilirubin: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

SGOT: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Vitamin E: ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

ANA (antinuclear antibody): ___ Normal ___ Abnormal ___ Unsure ___ Not done

Date: _____

Comments: _____

Biopsies:

Was a nerve biopsy performed?

- ☐ Yes
- ☐ No
- ☐ Unsure

If yes, characterize the results:

- ☐ Normal
- ☐ Abnormal
- ☐ Unsure

Comment: _____

Was a muscle biopsy performed?

- ☐ Yes
- ☐ No
- ☐ Unsure

If yes, characterize the results:

- ☐ Normal
- ☐ Abnormal
- ☐ Unsure

Comment: _____

Abstractor Information

Abstractor Name: _____

Abstractor Signature: _____

Date: _____

Abstractor Comments:

Remainder of Form to be Completed by Consulting Neurologist

ALS Diagnosis:

El Escorial Criteria: ☐ Clinically definite ALS
☐ Clinically probable ALS
☐ Clinically probable – Laboratory supported ALS
☐ Clinically possible ALS
☐ Clinically suspected ALS
☐ Not ALS

Comments:

Neurologist Name: _____

Neurologist Signature: _____

Date: _____

Appendix 4: Patient Surveillance Forms

MS/ALS Advocacy Group

Address

Date

Patient Name

Address

Dear _____:

We are writing to you regarding a request for your participation in a surveillance project being conducted by the Massachusetts Department of Public Health (MDPH).

The purpose of the MDPH surveillance project is to estimate the prevalence of Multiple Sclerosis and Amyotrophic Lateral Sclerosis in southeastern Massachusetts. The MDPH has been awarded federal monies from the Agency for Toxic Substances and Disease Registry (ATSDR) to estimate the prevalence of these diseases and to examine the estimates in relation to sources of environmental contamination in southeastern Massachusetts.

To estimate prevalence, the MDPH will need to identify all individuals who have resided in the surveillance area since January 1, 1998 and who have been identified by their neurologist as having MS or ALS. MDPH has asked [advocacy group name] to help identify individuals who might be eligible for inclusion in the surveillance. We are writing to ask your permission to give MDPH your name as someone who would be willing to participate if eligible for inclusion.

Once individuals have been identified and they have given informed consent for their participation, the MDPH's trained medical record abstractors will contact the office of the individual's neurologist, to request to review and abstract information from the individual's medical record. The medical record will never leave the office. Under federal privacy regulations, promulgated to comply with the Health Insurance Portability and Accountability Act (HIPAA), and state confidentiality and privacy regulations promulgated to comply with Massachusetts General Laws c.111, s.24A, the MDPH is required to keep all protected health information collected strictly confidential. Furthermore, MDPH employees are required to sign a pledge of confidentiality to assure patient privacy. This pledge requires employees to voluntarily cease employment should they ever reveal a patient's name or identifying information to anyone other than those conducting surveillance.

For most individuals in the surveillance project, the type of information that will be extracted from their record will include only what is necessary to confirm a diagnosis of MS or ALS and their community of residence during the surveillance period. Additional personal information that will be extracted includes date of birth, race, date of diagnosis, and determination of whether an office visit occurred anytime during the six-year period 1998 through 2003. For a sample of individuals, an independent neurologist will verify the diagnosis through a complete record review, reviewing information related to diagnostic criteria used by neurologists. This step is necessary to evaluate the accuracy of the record abstraction process.

All information collected as part of the surveillance will be kept strictly confidential in accordance with the laws and regulations of the Commonwealth.

[insert name of advocacy group] fully supports the MDPH effort to better understand the occurrence of MS and ALS in our state. Please do not hesitate to call our office if you have any questions. If you would like to participate in the surveillance, please complete the short questionnaire attached and read and sign the authorization for disclosure of medical information, and then return these forms to the MDPH in the enclosed, pre-addressed stamped envelope. Thank you for your time.

The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

MITT ROMNEY
GOVERNOR

KERRY HEALEY
LIEUTENANT GOVERNOR

RONALD PRESTON
SECRETARY

CHRISTINE C. FERGUSON
COMMISSIONER

**AUTHORIZATION FOR
DISCLOSURE OF MEDICAL INFORMATION**

I agree to allow the Massachusetts Department of Public Health and their medical consultant to review my medical records, as described below, in an attempt to confirm diagnosis of my disease and to investigate relevant information that may be available in my records. I understand that this task aims to estimate disease prevalence and explore possible risk factors. I understand that my agreement to authorize the disclosure of my medical information is completely voluntary. I also understand that I may revoke this authorization at any time by making a request in writing to Robert S. Knorr at the Department of Public Health, 250 Washington Street, Boston, MA 02108. The revocation will apply only to future releases of confidential information in my medical records after the date of my revocation.

I agree to cooperate with the Massachusetts Department of Public Health by allowing my medical records, including identifying information, in the possession of my physician, or any hospital, clinic, or other health care facility at which I was diagnosed or treated, to be inspected and/or photocopied by authorized research personnel working for the Bureau of Environmental Health Assessment (Suzanne Condon, Assistant Commissioner). This authorization covers all of my medical records, including records of medical treatment and history of illness or related information. In addition, it allows for a medical consultant working under contract with the Massachusetts Department of Public Health to discuss such medical information directly with my physician. The expiration date for this authorization is at the completion of the study.

It is my understanding that all information collected will be kept strictly confidential in accordance with the laws and regulations of the Commonwealth of Massachusetts relating to confidentiality and privacy.

I hereby authorize the following medical office or clinic where I was diagnosed or treated:

(Name and location): _____
to release information from my medical records to the Massachusetts Department of Public Health.

Patient's Name (please print clearly) _____

Signature _____ Date _____

**Prevalence of Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) in
Southeastern Massachusetts**

**Epidemiological Surveillance by the
Massachusetts Department of Public Health
And
Agency for Toxic Substances and Disease Registry**

Please complete this form and return to Jan Sullivan, Massachusetts Department of Public Health, Bureau of Environmental Health Assessment, 250 Washington St., Boston, MA 02108-4619, using the enclosed prepaid, self-addressed envelope. If you have any questions, please call us at [insert organization's number] or Jan Sullivan at MDPH at 617 624-5757.

Name of patient: _____

Address of patient: _____

Have you been diagnosed with ALS or MS? ___ Yes ___ No ___ Probable
(please circle MS or ALS)

*Note: Surveillance covers the period January 1, 1998 through December 31, 2003. We will include individuals who resided during this period in our surveillance area and whose medical record indicates a diagnosis of ALS or MS (as definite or probable) **before** or **during** the surveillance period.*

Did you reside in the surveillance area (see attached town list) between January 1, 1998 and December 31, 2003? ___ Yes ___ No

If yes, please provide the name of your neurologist or medical clinic where you have been treated for MS/ALS:

Name: _____

Address: _____

Comments: _____

Appendix 5: Patient Self Referral Form

Patient Self-Referral Form, MS/ALS Prevalence Project

Directions: When a patient calls in, please obtain the following information only if the patient has been told that he/she has been diagnosed with Amyotrophic Lateral Sclerosis (ALS) or Multiple Sclerosis (MS) and was a resident of the surveillance area at any time since January 1, 1998. Patients' address will be used to send the Authorization for Disclosure of Medical Information form authorizing review of medical records for those self-identified as having MS or ALS.

Resident of Surveillance Area at any time since January 1, 1998? (please circle)	Diagnosis (please circle)	Patient Name/Address/Phone	Date of Birth	Provider/Medical Record Facility
Yes No	ALS MS		____/____/____	Provider Name: _____ Address: _____ Phone # _____
Yes No	ALS MS		____/____/____	Provider Name: _____ Address: _____ Phone # _____
Yes No	ALS MS		____/____/____	Provider Name: _____ Address: _____ Phone # _____
Yes No	ALS MS		____/____/____	Provider Name: _____ Address: _____ Phone # _____
Yes No	ALS MS		____/____/____	Provider Name: _____ Address: _____ Phone # _____
Yes No	ALS MS		____/____/____	Provider Name: _____ Address: _____ Phone # _____

Appendix 6: 1993-2003 ALS Prevalence by Community

1998 – 2003 ALS Period Prevalence by Community

<i>Surveillance Area Communities</i>	<i>ALS Prevalence</i>		
	Number of cases	Population	Prevalence per 100,000 Population (CI*)
Abington	3	14,605	20.5 (4.2-60.0)
Bridgewater	1	25,185	4.0 (0.1-22.1)
Brockton	3	94,304	3.2 (0.7-9.3)
Carver	2	11,163	17.9 (2.2-64.7)
Cohasset	1	7,261	13.8 (0.4-76.7)
Duxbury	5	14,248	35.1 (11.4-81.8)
East Bridgewater	1	12,974	7.7 (0.2-42.9)
Halifax	0	7,500	-
Hanover	2	13,164	15.2 (1.8-54.8)
Hanson	0	9,495	-
Hingham	1	19,882	5.0 (0.1-28.0)
Hull	3	11,050	27.2 (5.6-79.3)
Kingston	1	11,780	8.5 (0.2-47.3)
Lakeville	1	9,821	10.2 (0.3-56.7)
Marion	0	5,123	-
Marshfield	2	24,324	8.2 (1.0-29.7)
Mattapoisett	0	6,268	-
Middleborough	0	19,941	-
Norwell	0	9,765	-
Pembroke	1	16,927	5.9 (0.2-32.9)
Plymouth	5	51,701	9.7 (3.1-22.5)
Plympton	0	2,637	-
Raynham	1	11,739	8.5 (4.2-47.4)
Rochester	0	4,581	-
Rockland	3	17,670	17.0 (3.5-49.6)
Scituate	2	17,863	11.2 (1.4-40.4)
Wareham	0	20,335	-
West Bridgewater	0	6,634	-
Weymouth	4	53,988	7.4 (2.0-19.0)
Whitman	1	13,882	7.2 (0.2-40.1)
TOTAL	43	545,810	7.9 (5.7-10.6)

* CI = 95% Confidence Interval (lower limit–upper limit).

Appendix 7: 1998-2003 MS Prevalence by Community

1998 - 2003 MS Period Prevalence by Community

<i>Surveillance Area Communities</i>	<i>MS Prevalence</i>		
	Number of cases	Population	Prevalence per 100,000 Population (CI*)
Abington	27	14,605	184.9 (121.8-269.9)
Bridgewater	26	25,185	103.2 (67.4-151.8)
Brockton	116	94,304	123.0 (102.1-148.1)
Carver	19	11,163	170.2 (102.5-265.5)
Cohasset	12	7,261	165.3 (85.4-289.2)
Duxbury	15	14,248	105.3 (59.0-173.7)
East Bridgewater	25	12,974	192.7 (124.7-285.2)
Halifax	15	7,500	200.0 (112.0-330.0)
Hanover	29	13,164	220.3 (147.6-317.2)
Hanson	16	9,495	168.5 (96.4-273.0)
Hingham	25	19,882	125.7 (81.4-186.1)
Hull	10	11,050	90.5 (43.4-166.5)
Kingston	24	11,780	203.7 (130.6-303.7)
Lakeville	12	9,821	122.2 (63.2-213.8)
Marion	5	5,123	97.6 (31.6-227.4)
Marshfield	34	24,324	139.8 (96.8-195.4)
Mattapoisett	9	6,268	143.6 (65.8-272.8)
Middleborough	25	19,941	125.4 (81.1-185.6)
Norwell	20	9,765	204.8 (125.1-315.4)
Pembroke	23	16,927	135.9 (86.2-203.8)
Plymouth	80	51,701	152.8 (123.5-193.4)
Plympton	2	2,637	75.8 (9.2-273.8)
Raynham	22	11,739	187.4 (117.5-283.0)
Rochester	1	4,581	21.8 (0.6-121.6)
Rockland	27	17,670	152.8 (100.7-223.1)
Scituate	28	17,863	156.8 (104.2-227.3)
Wareham	22	20,335	108.2 (67.8-163.4)
West Bridgewater	8	6,634	120.6 (52.0-237.6)
Weymouth	101	53,988	187.1 (153.2-278.1)
Whitman	22	13,882	158.5 (99.4-239.3)
TOTAL	800	545,810	146.4 (136.6-157.1)

* CI = 95% Confidence Interval (lower limit-upper limit).