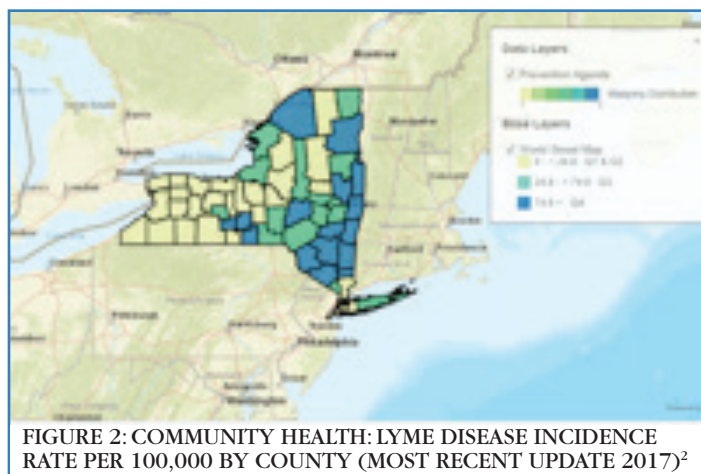
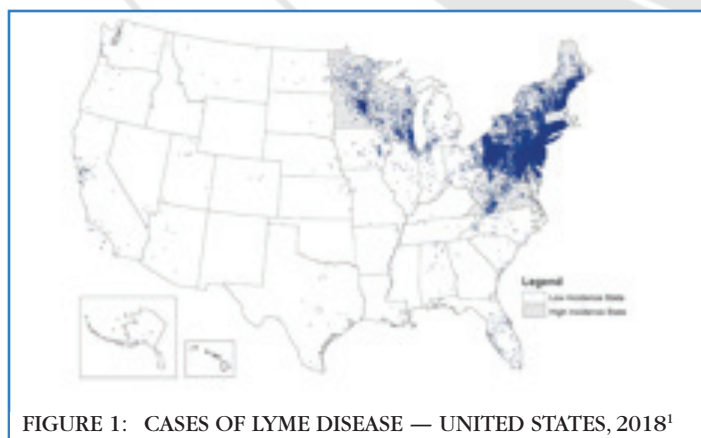


Northeastern Climate is Bullseye for Lyme Disease

By Moshe Bressler; Patricia Happel, DO; William Blazey, DO; Orit Markowitz, MD and Emily Senay, MD, MPH

Background, Incidence and Climate Change

With spring upon us and after a record warm winter, this is a good time to review the manifestations, treatments, and drivers of Lyme disease (LD) – the most common vector-borne disease in the United States (US). New York family physicians are on the front line of this growing threat as the highest incidence of LD is found in the American Northeast corridor, including the states of New York, Connecticut, and Pennsylvania (Figure 1).¹

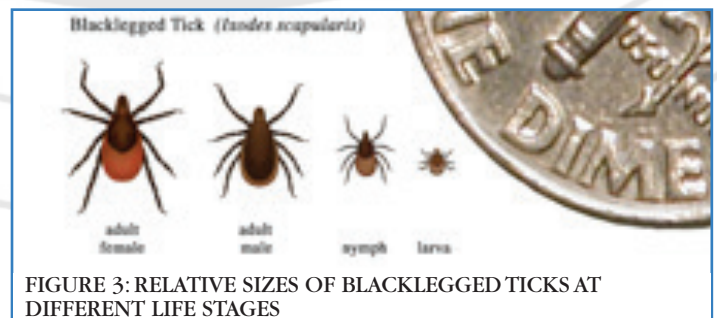


Over the past few decades, New York has seen substantial growth in Lyme cases (> 400% between 2012-17 in some parts of the state²), and the incidence is projected to continue rising. In 2018, there were 2886 confirmed or suspected LD cases in New York State (NYS) and 752 in New York City.³ NYS community health data show wide variability in incidence by county.⁴ (Figure 2)²

Despite mandatory reporting in NYS,⁵ it is believed only a fraction of cases are reported to public health authorities.⁶ Nationally, the CDC estimates less than 10% of cases are reported;⁷ therefore, the actual incidence of LD in NYS and nationally is unknown, with total US cases

estimated to be as high as 300,000 per year. Despite limitations related to reporting, it is clear that cases of LD have steadily risen over the past two decades.⁸

LD is caused by the bacterium *Borrelia burgdorferi*, which is carried by *Ixodes scapularis*, the blacklegged tick,⁹ also known as the deer tick. The lifecycle of blacklegged ticks requires three different vertebrate hosts, including the white-footed mouse, the most common reservoir for *Borrelia burgdorferi*. While black-legged ticks feed on deer in the adult stage, deer are not reservoirs of the borrelia bacterium.¹⁰ Most humans are infected via immature nymph ticks primarily because their small size makes them harder to detect and remove before the bacteria can be transmitted which takes 36 to 48 hours.^{8,10} (Figure 3)¹⁰



Many factors can influence the distribution, transmission, and incidence of LD. Evidence points to climate change, especially warming temperatures and increased humidity,¹¹ as an important factor in the range expansion northward into areas where the *Ixodes scapularis* tick was previously unable to survive.¹² Because tick activity depends on temperatures above a certain minimum, shorter winters can also lengthen the period ticks are active and able to infect humans.⁸ Other ecosystem disturbances such as changes in host populations of deer and white-footed mice¹¹ as well as human proximity to ticks can increase or decrease LD cases.⁸

Lyme Disease Presentation

Early localized disease presents with the pathognomonic bullseye rash otherwise known as erythema migrans (EM), developing in 70-80%¹³ of patients with LD, at the site of the tick bite in the following days-weeks after initial inoculation.¹⁴ Removing attached ticks and species identification is described later in this article.

Physicians should examine the patient's entire body; recent studies show up to 23% of patients with EM are initially missed.¹⁵ Lesions typically develop at the tick bite site,¹⁶ especially on the lower legs and upper trunk.¹⁷ EM typically develops on the trunk, groin, intertriginous region, and head and neck in children.¹⁸ Multiple smaller EM lesions are the earliest sign of disseminated disease.¹⁸

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EM presents as “bullseye” rash with a central clearing and large steady expansion in the following days, which differentiates from an allergic reaction to bug bites, presenting as annular edematous papules with a central hemorrhagic punctum.¹⁹ The most common co-presenting symptoms are fatigue (54%), myalgias (44%), arthralgias (44%), headache (42%), and neck stiffness (35%).²⁰ Upper respiratory symptoms and gastrointestinal symptoms point to an alternative etiology.²¹ LD should be considered in patients presenting with a “summertime cold.”

Early disseminated disease is a result of the spirochete migrating throughout the host causing acute reactions in multiple organs.¹⁴ Symptoms develop in weeks to months and include meningitis, unilateral or bilateral Bell’s Palsy, radiculopathies, ocular manifestations, carditis, 3rd-degree heart block, multiple EM lesions, and migratory arthralgias.¹⁴

Late disease develops in months to years in untreated cases. Similar to other tertiary spirochete syndromes, symptoms include intermittent or chronic arthritis, neurological disease, and cutaneous involvement (*only in European variant) usually presenting in a unilateral distribution.¹⁴ Arthritis, especially in the knee, is the most common presentation for late LD.¹⁴

Up-to-date Diagnosis of Lyme

Clinical Workup:

In early localized LD with EM, the diagnosis is clinical, if the exposure was in an endemic area.²² Serological testing is not recommended in early cases since it will take 2-4 weeks of untreated LD to develop sufficient antibody levels. Only 20%-40% of patients at this stage will be seropositive.²³ Testing after treatment is not recommended either since patients treated with antibiotics early in the disease course will not develop an antibody response.

In early disseminated and late Lyme disease, the diagnosis is made with serological testing *only in the context of clinical symptoms*²⁴ (figure 4) since IgM and IgG levels can persist for years after initial infection and false-positives on serology are common.

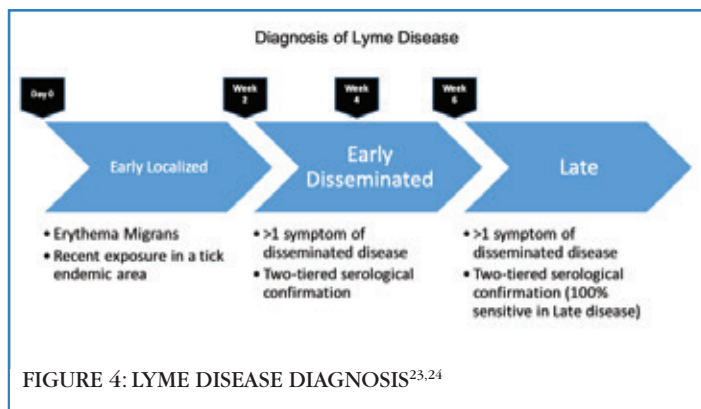


FIGURE 4: LYME DISEASE DIAGNOSIS^{23,24}

Serology will be positive in all patients with LD arthritis.²⁴ Synovial fluid arthrocentesis is not recommended, but if performed, will show many white blood cells (WBC) ranging from 10,000-25,000.²⁴ Culture is difficult and not recommended. Diagnosis is made via serological testing taken from the serum.

In severe cases of neurologic involvement where encephalitis or meningitis is suspected, lumbar puncture is mandatory to rule out other more dangerous pathogens. Analysis of cerebral spinal fluid (CSF) will show moderate pleocytosis of lymphocytes/monocytes in the several hundred /microL, moderately elevated protein (up to 300 mg/dL), and glucose within normal range.²⁵ Interestingly this profile is similar to multiple myeloma; thus, clinical correlation and environmental exposure are essential to clinical workup. CSF can be tested for antibodies against *B. burgdorferi*, however sensitivity is low and a negative test does not rule out disease.²⁶

Laboratory Workup:

Diagnosing LD uses a two-tiered approach and starts with a sensitive enzyme immunoassay (EIA) or immunofluorescence assay (IFA) followed by a Western blot. As of 2019, the CDC approved EIA as an option for the confirming step.²⁷ Most laboratories still use western blot as the confirm step.

Reflex testing is available by labs such as Quest Diagnostics (test number 6646²⁸) and Labcorp (test number 258004²⁹) which requires one lab draw and confirms via western blot reflexively only if the initial test is positive. Testing for multiple tick-borne illnesses simultaneously via PCR is also available from select laboratories; Accutix, offered by Imugen, tests the pathogens prevalent in specific regions.³⁰

Types of Tests:

EIAs include ELISA (enzyme-linked immunosorbent assay) which test for IgG and IgM antibodies to specific proteins from *Borrelia burgdorferi*. The antibody tests listed require 1-2 mL of serum; clinicians should draw 2.5 times the requested amount, allow blood to coagulate for 60 minutes and centrifuge.³¹ The specimen should be transported at room temperature, and there is an estimated 1-4 day turnaround; the costs range from \$55 to \$200 USD.³²

- *Whole-cell ELISA*: highly sensitive but false positives are common (5% of US population will test positive).²³
- *VisE C6 ELISA*: sensitive with fewer cross-reactants. See chart below (figure 5²³) for comparison.
- *Immunofluorescence assay (IFA)*: sensitive for screening patients with LD however poor specificity has resulted in decreased utilization.³³
- *Western blot (or immunoblot)*: detects a multitude of different antibodies and is highly specific. Reading western blot results requires skill and training, limiting its use. Additionally, indeterminate results are common.³³

Tests Not Recommended:

The CDC does not recommend using capture assay for urine antigens, testing synovial fluid for borrelia antibodies, or in-house criteria for immunoblot interpretation; as these tests are non-specific and unreliable.³⁴ Culture is extremely lengthy, difficult, and usually unavailable.²³

Species confirmation of removed ticks is helpful in clinically managing LD,³⁵ however testing ticks for *B. Burgdorferi* is not recommended as it will not guide treatment; <36 hours will not

clinical presentation.²⁴ This workup additionally applies to previously vaccinated patients and may show false positives on serology.²⁴

Post-Lyme Disease Syndrome (PLDS), or post-Lyme arthritis, will display high IgM and IgG titers during the manifestation of disease; these may circulate for years after the symptoms resolve. It is believed these antibodies offer protection to reinfection, therefore clinical manifestations should steer clinicians to diagnosis.²⁶ Current tests may confuse other tick-borne illnesses such as STARI or *Borrelia miyamotoi*³⁸ however both are treated similarly to LD (see table 1).

Current Treatment for Lyme and Post Exposure Prophylaxis*

Tick bite prophylaxis is warranted (see table 1) if all the following criteria are met: (a) nymph attachment is >36 hours but less than 72 hours (b) the tick can be identified as *Ixodes Scapularis* (c) LD is common in the region of exposure (CT, DE, DC, MA, MD, ME, MN, NH, NJ, NY, PA, RI, VA, VT, WI, WV).^{24, 39}

The CDC considers the following three scenarios confirmed cases of Lyme Disease:²²

1. EM with recent tick exposure (<30 days) in a high incidence state (see above).
2. EM with confirmed laboratory evidence (with 2 tier algorithm).
3. At least one late manifestation and confirmed laboratory evidence.

Common Co-infections, Post Lyme Disease Syndrome

Post Lyme Disease Syndrome (PLDS) is the development of headache, neurocognitive difficulties, fatigue, or diffuse pain lasting >6 months following treatment of *confirmed* Lyme disease by two-tiered serological testing or documented EM by a qualified health professional.⁴⁰ Important

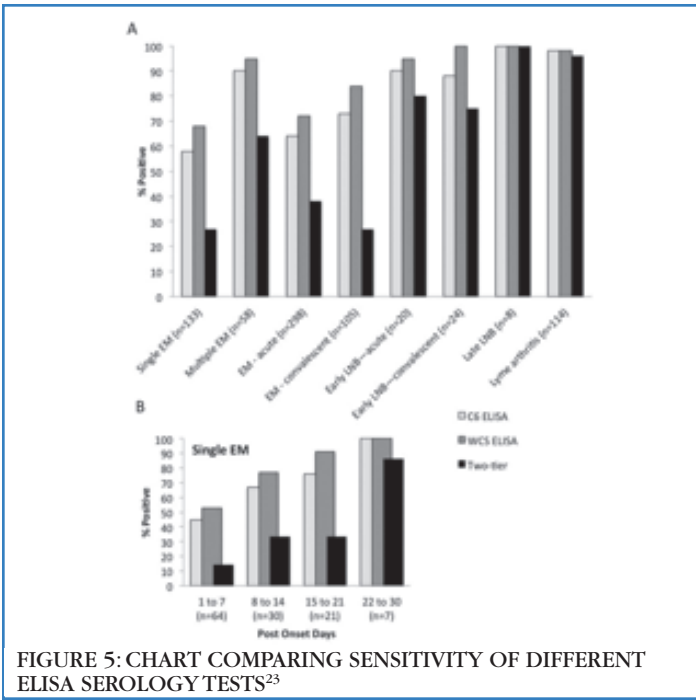


FIGURE 5: CHART COMPARING SENSITIVITY OF DIFFERENT ELISA SEROLOGY TESTS²³

transfer disease, >36 hours warrants empiric treatment and testing will only delay treatment.³⁶

Limits of Testing:

Due to high rates of false positives, laboratory testing alone should not guide treatment, only symptomatic patients (either EM or late disease manifestation) are considered to have LD.²² Routine annual laboratory testing for LD is *not* recommended, as per the CDC.³⁷

Previously infected patients may test positive for years after clearing infection, and in these cases, the diagnosis should be made based on

Table 1: Lyme Disease Treatment Indications^{24,40,41}

Disease State	Treatment*	Duration (days)
n/a	Prophylaxis	Adults: single dose of Doxycycline, 200mg; children > 8 years old single dose Doxycycline 4.4 mg/kg
Early Localized	Erythema Migrans	Oral regiment
Early Disseminated	Carditis	Oral regiment
	Isolated Nerve Palsies	Oral regiment
	Meningitis or Radiculopathy	Parenteral therapy
	Severe Carditis or Heart Block	Parenteral therapy
Late Disseminated	Lyme Arthritis	Oral regiment
	Persistent Lyme Arthritis Despite Oral Antibiotic Treatment	Alternative oral regiment or parenteral therapy
	Central Nervous System Disease	Parenteral therapy
Post Treatment	Post-Lyme Disease Syndrome	No antibiotics

*See table 2 for recommended adult and children therapies.

**Recent studies suggest the efficacy of shorter treatment courses in early Lyme disease³⁹.

Table 2: Recommended Antibiotics (in decreasing order of superiority)^{24,41,42}

	Adults	Children
Oral Treatment	Doxycycline, 100 mg PO, BID	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (max 200 mg/day)
	OR	OR
	Amoxicillin, 500 mg PO, TID	Amoxicillin, 50 mg/kg per day, orally, divided into 3 doses (max 1.5 g/day)
	OR	OR
	Cefuroxime axetil (Ceftin), 500 mg PO, BID	Cefuroxime, 30 mg/kg per day, orally, in 2 divided doses (max 1000 mg/day or 1 g/day)
	OR	OR
	Azithromycin (Zithromax), 500 mg PO QD	for a patient unable to take a beta-lactam or doxycycline, Azithromycin, 10 mg/kg/day, orally, once daily
Parental Therapy	Ceftriaxone (Rocephin), 2 g intravenously per day	Ceftriaxone, 50 to 75 mg per kg intravenously per day, single dose
	OR	
	Cefotaxime (Claforan), 2 g intravenously every eight hours	
Abbreviations: PO: By mouth; QD- once daily; BID- twice daily; TID- thrice daily		

to note, this syndrome is *not* a manifestation of ongoing Lyme disease, and the term “chronic Lyme disease” is a false and misleading misnomer.¹⁶ While patients may self-attribute neurological conditions and diffuse pain to PLDS, conversely, PLDS is a diagnosis of exclusion. Patients presenting with such symptoms should be evaluated for other neurological diseases such as multiple sclerosis or underlying malignancies.¹⁶ This condition can also be a manifestation of fibromyalgia.⁴³ Serology is often positive due to prior infection.⁴⁰

PLDS, by definition, is a confirmed case of LD, which has already been treated with appropriate drug therapies, and additional rounds of these medications should not be offered as treatment.¹⁶ This topic is of significant controversy due to public misinformation. Patient advocacy groups have formed to promote raising awareness for ‘chronic Lyme’ and self-refer to self-proclaimed Lyme specialists who offer unnecessary lengthy treatments of IV antibiotics, creating unnecessary risks and costs.¹⁶ PLDS tends to ebb and flow in severity and a long-term treatment plan should be formalized. Physicians should address patients with a team-building agenda and offer to combat misinformation with compassion.

European strains of *Borrelia* consist of a variety of strains and tend to have greater severity of initial presenting illness. Immunity to American LD is not protective against European LD and vice versa. Field scientists spending long durations of time in tick-infested woodlands have noted immunity to tick attachment⁴⁴ however this is not a recommended prevention method.

LD can present with other comorbid tick-borne illnesses, including *Borrelia miyamotoi*, babesiosis, and anaplasmosis. Many of these are also carried by the blacklegged tick and treatment of LD with doxycycline covers all of these pathogens, making it the preferred treatment for tick-borne illnesses.⁴⁵ Southern tick-associated rash

illness (STARI) can also co-present with LD and is carried by the lone star tick which used to be isolated to the Southeastern US. Habitat expansion is favoring a northern migration and several cases have been reported in NYS residents.³⁸ Of most alarm, STARI can induce an allergic reaction which induces permanent red-meat allergy.³⁸

NIAID-funded researchers recently published on a multiplex serological platform that can simultaneously detect up to eight tick-borne diseases from a single patient sample at the point-of-care.⁴⁶ This test is currently under development and will a valuable tool for physicians once made readily available.

Prevention, Tick Management, and Reporting Disease to Health Officials

A vaccine to prevent Lyme Disease is being developed, however it will not likely be available until after 2022.⁴⁷ The only other current methods of prevention include wearing preventative clothing, using insect repellants, early tick removal, and proper patient education. Hikers should cover up with long sleeve shirts and long pants tucked into socks. Insect repellents are a safe and easy option that can be applied both on skin and clothing. The CDC and EPA recommend products with >20% DEET⁴⁸ or Picaridin [Cutter Advanced™]. Care should be given to avoid ingestion, and repellents should not be sprayed near the eyes, nose, or mouth. When applying on children, repellent should be first sprayed on adult hands and then rubbed on children’s faces. Toxicity is rare and typically occurs with ingesting insecticide. Commercial insecticide sprays are an inexpensive and safe option, especially when compared to “DIY homemade insect repellent sprays,” which usually consist of lemon eucalyptus oil or other essential oils;⁴⁹ these can cause adverse skin reactions especially in young children.⁴¹ Insect repellent sprays typically require reapplication every 4-6 hours, and more dedicated outdoor enthusiasts can consider permethrin-treated clothing, which offers constant protection but

requires strict adherence to instructions before initial use. Treated clothing will offer protection for up to 70 laundry cycles.⁴⁹

Tick removal can be performed in-office or at home. Lidocaine can be applied directly to the tick to weaken its attachment.³⁵ Using fine-tipped forceps, the tick should be grasped delicately close to the skin, where the tick is latched (see figure 5). Steady even pressure in an upward motion will remove the tick. Take care to avoid crushing the tick as *B. burgdorferi* may be lurking inside.³⁶ Preserve the tick in 70% alcohol in a well-sealed container so the species can be identified later with a dermatoscope or microscope.³⁵



FIGURE 6: MANUAL TICK REMOVAL ILLUSTRATION (IMAGE SOURCE: CONSUMER REPORTS)

Lyme disease surveillance and epidemiological data have been limited by underreporting of cases. Not only is Lyme disease a mandated reportable illness, doing so will spur public health efforts forward. LD is a reportable disease, as outlined by the CDC's case definition.²² Cases should be reported to the local health department [forms, directory, and other helpful reporting links can be accessed via the NYS Department of Health website⁵]. We earlier mentioned the CDC outlines mandated reporting for confirmed cases, defined by EM with recent tick exposure (<30 days) in high incidence state (NY, NJ, CN, and PA are all high incidence states), EM with laboratory evidence, or late manifestation of disease with laboratory evidence.²²

Conclusion

Physicians should be ready to recognize and treat Lyme appropriately and to educate patients about tick-borne illnesses, especially with pet owners or outdoor enthusiasts living in tick-infested regions (see sample in supplement 1).⁴⁸ Misinformation tends to be highly infectious and can cause more widespread devastation than the actual disease.

Endnotes

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Lyme and Tick Prevention

By Dr. Orit Markowitz MD

The best way to prevent Lyme disease is to avoid areas where deer ticks live, especially wooded, bushy areas with long grass. You can decrease your risk of getting Lyme disease with some simple precautions:

- **Protect yourself.** When in wooded or grassy areas, wear shoes, long pants tucked into your socks, a long-sleeved shirt, a hat and gloves. Walk in the center of trails and avoid walking through tall bushes or other vegetation. Keep your dog on a leash.
- **Use insect repellents.** Apply insect repellent with a 20 percent or higher concentration of DEET to your outer clothing or skin. Avoid spraying in your eyes and mouth.
- **Shower right away.** Ticks often remain on your skin for hours before attaching themselves. A tick usually must be attached for greater than 24 hours to successfully infect you with Lyme Disease.
- **Do your best to tick-proof your yard.** Clear brush and leaves where ticks live. Mow your lawn regularly. Stack wood neatly in dry, sunny areas to discourage rodents that carry ticks.
- **Check: yourself, your family and your pets for ticks.** Be especially vigilant after spending time in wooded or grassy areas. Deer ticks are often no bigger than the head of a pin, so you might not discover them unless you search carefully.
- **Remove a tick as soon as possible with tweezers.** (or go to an urgent care for professional removal)
- **Be alert for fever or rash.** Even if you don't remember being bitten by a tick. An unexpected summer fever or odd rash may be the first signs of Lyme disease, particularly if you've been in tick habitat. Contact your dermatologist or general practitioner immediately.
- **Don't assume you're immune.** You can get Lyme disease more than once.

SUPPLEMENT 1: HANDOUT USED IN THE AUTHOR'S DERMATOLOGY CLINIC

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Moshe Bressler, BS is attending the NYIT College of Osteopathic Medicine, Department of Family Medicine in Old Westbury, NY

Patricia Happel, DO is affiliated with the NYIT College of Osteopathic Medicine, Department of Family Medicine in Old Westbury, NY

William Blazey, DO is affiliated with the NYIT College of Osteopathic Medicine, Department of Family Medicine, Old Westbury, NY

Orit Markowitz, MD is affiliated with the Icabn School of Medicine at Mount Sinai, Department of Dermatology, New York, NY

Emily Senay, MD, MPH is affiliated with the Icabn School of Medicine at Mount Sinai, Department of Environmental Medicine & Public Health, New York, NY