Proposal for Conducting Sentinel Surveillance for Extrapulmonary Nontuberculous Mycobacteria (ENTM) under the Minnesota Communicable Disease Rule (4605.7046)

Division: Infectious Disease Epidemiology, Prevention and Control Division

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Under part 4605.7046 of the Communicable Disease Reporting Rule, the Commissioner may select infectious diseases/syndromes and reporting sites for sentinel surveillance if the specified criteria are met. The law specifically says:

"Subpart 1. **Disease selection**. The commissioner may select an infectious disease or syndrome for sentinel surveillance, other than a disease or syndrome for which general reporting is required under this chapter, if the commissioner determines that sentinel surveillance will provide adequate data for epidemiological purposes and the surveillance is necessary for:

A. characterization of the pathogen;
B. monitoring vaccine effectiveness; or
C. achieving other significant public health purposes for a disease or syndrome that can cause serious morbidity or mortality.

Subp 2. **Site selection**. The commissioner shall select, after consultation with the sites, sentinel surveillance sites that have epidemiological significance to each disease or syndrome selected under subpart 1. In selecting the sites, the commissioner shall consider:

A. the potential number of cases at the site;
B. the geographic distribution of cases or potential cases in Minnesota, if indicated by the epidemiology of the disease or syndrome;
C. the epidemiology of the disease or syndrome; and
D. the overall impact of sentinel surveillance on a site and the benefit to public health in conducting sentinel surveillance at the site."

1. DISEASE SELECTION

A. Will population-based sentinel surveillance provide adequate data for epidemiological purposes, specifically characterization of the pathogen or achieving other significant public health purposes for a disease or syndrome that can cause serious morbidity or mortality?

Nontuberculous mycobacteria (NTM) are widespread and naturally occurring in the environment, especially in soil and water, from which humans may acquire these organisms.[1] NTM are opportunistic pathogens that have a strong affinity for infecting patients in health care settings. The potable water systems that supply many U.S. health care facilities are excellent reservoirs for NTM to occur naturally. In both hospitals and clinics NTM can find opportunities to infect immunocompromised patients due to breaches in patients' natural defenses such as medical devices. Healthcare-associated transmission has occurred due to contaminated medical equipment or solutions that contain water.[2] NTM causes both pulmonary and extrapulmonary disease, depending on the body site of the infection. Extrapulmonary nontuberculous mycobacteria (ENTM) is less common and occurs in any body site outside of the lungs and may result from direct inoculation. ENTM can cause an extremely broad range of infections that vary depending on the specific NTM species and the person who is infected. The incubation period of NTM infection varies depending on the mycobacterium species, exposure, and disease manifestations, and can extend from several weeks to possibly five years.[3] Extrapulmonary infections include cervical lymphadenitis, an enlargement of the lymph nodes that predominantly occurs in young children; disseminated infection, which occurs in immunosuppressed patients that requires treatment with long and complicated regimens of antibiotic drugs; and opportunistic disease, which occurs as a result of contamination of NTM from the environment or health care equipment and most often seen as an infected skin wound, a soft tissue infection or a prosthetic joint infection.[4] ENTM infections can cause a wide variety of symptoms; the specific symptoms of ENTM infection will depend on the site the bacterium entered the body and the individual infected.

Almost 200 species of NTM have been identified, but less than 20 commonly cause human infections.[5] NTM species are divided based on their growth speed and presence of pigment on laboratory media.[6] NTM commonly form biofilms, which are a thin film of bacteria that adhere to surfaces in the environment, and can be highly resistant to disinfectants.[7] Strict infection control and prevention practices are critical to the identification and cessation of ENTM outbreaks. This however, can often prove incredibly difficult given the ubiquitous nature of many ENTM species, and many standard infection control practices are not always effective against NTM.[8]

ENTM infections can be among the most challenging cases that physicians face. Many cases are not diagnosed during initial symptom presentation; correct diagnosis at the first physician visit is often very difficult. Identification of ENTM requires special laboratory equipment and techniques. As treatment will be based on the species of mycobacteria, it is important that all human infections with mycobacteria are cultured.

A lack of culture and identification could affect patient outcome.[9] Treatment regimens vary, but typically involve multiple antibiotics for long durations and may sometimes involve surgical excision, in the setting of surgical site infections.[10]

The prevalence of human disease caused by ENTM has increased over the last decade. Whether the increase in cases is real or whether more cases are being recognized and diagnosed remains unclear due to a lack of surveillance for ENTM. Outbreaks in a variety of health care settings of ENTM have occurred causing serious morbidity and mortality. A widely publicized outbreak due to prosthetic valve endocarditis and other invasive disease caused by *M. chimaera*. This global outbreak from 2011 to 2016 was traced to contamination of water heater-cooler units used during open-heart surgery. In the United States, half a million patients were exposed and 11 deaths occurred.[11] Other recent national outbreaks include *M. abscessum* infections in 20 children as a result of contaminated dental water lines in California in 2016[12] and an outbreak of *M. fortuitum* infections associated with a tattoo parlour.[13] In addition to the outbreaks occurring in the United States, increases in medical tourism for cosmetic surgery outside of the United States have led to outbreaks of ENTM. Many of these surgeries and procedures involve the removal of fat or breast augmentation in developing nations. The scope of these outbreaks due to medical tourism are largely unknown, as identification of infection needs to be based on mandatory case reporting. Skin and soft tissue infections due to NTM are believed to be increasing but still underdiagnosed. Detection of ENTM outbreaks will often be delayed when the condition is not reportable.[10]

In Minnesota, infections with ENTM are not reportable under the Minnesota Communicable Disease Rules; however in December of 2016, a dermatologist voluntarily notified the Minnesota Department of Health (MDH) of three Minnesota patients with skin lesions after self-administration of human chorionic gonadotropin (HCG) injections. The same weight loss clinic supplied all of the HCG injections. In total, MDH discovered six cases with illness onset dates ranging from April to November 2016. All patients were adult women who did not share HCG vials. All isolates taken from known cases were identified as *M. chelonae* that were indistinguishable by PFGE, which is a laboratory technique used to produce a DNA fingerprint for a bacterial isolate.[14] During the worldwide outbreak of *M. chimaera* prosthetic valve endocarditis, three of the outbreak cases occurred in MN residents.[15] One Minnesota specific study described a three-fold increase in cutaneous infections due to rapidly growing mycobacteria in Olmsted county from 1980 to 2006. The study found there were 40 identified infections during this period and many were associated with traumatic injuries. In separate review of prosthetic joint infections during 1969 to 2006 at Mayo Clinic, Eid et al. described nine infections that were associated with rapidly growing mycobacteria, and recommended that NTM be considered in infected prosthetic join infections that have negative routine cultures.[16]

Surveillance will include reporting from any laboratory that can identify NTM outside of the lungs among Minnesota residents. This laboratory data will produce sufficient information to monitor ENTM trends and antibiotic resistance in NTM. The surveillance will assess the burden of ENTM among Minnesota residents and allow MDH to better

understand the epidemiology of ENTM and associated risks in Minnesota. The prevalence of human disease caused by ENTM has increased over the last decade. Outbreaks in a variety of health care settings of ENTM have occurred causing serious morbidity. Implementing sentinel laboratory surveillance will enable MDH to assess the burden of disease and trends, as well as identify potential outbreaks due to ENTM.

B. Why is the surveillance necessary?

MDH lacks a systematic method of collecting and studying the incidence and prevalence of ENTM, as well as the means to track antibiotic resistance in ENTM. Further, surveillance will enable the identification of possible outbreaks due to ENTM and help MDH assess the burden of disease and trends. The lack of surveillance impedes MDH's ability to monitor, prevent, and control ENTM and protect the health of Minnesota residents. As described above, national studies have found the prevalence of ENTM to be increasing, along with numerous outbreaks of ENTM occurring globally. Sentinel surveillance will provide data for assessing the incidence and prevalence of ENTM, tracking any potential increase in ENTM cases, along with observing the types of infections and demographics and clinical characteristics of the patients and their outcomes.

Objectives of this sentinel surveillance:

1. Determine and monitor the incidence, prevalence, and burden of ENTM in Minnesota.
2. Assess the risk factors for ENTM infection.
3. Describe the epidemiology of ENTM among Minnesota residents and assess any increase in cases, as seen in the national and global trends.
4. Identify and assess outbreaks of ENTM.

2. SITE SELECTION

A. Did you consult with the selected site(s)? Explain.

MDH contacted clinical laboratories in Minnesota by email to introduce ENTM surveillance and request feedback about the proposed surveillance program. We described the justification for surveillance. We explained that MDH staff will perform chart reviews to complete case report forms to not create an extra burden on the laboratories. There were no issues or concerns raised by health care facilities or clinical laboratories.

B. Does the site(s) have epidemiological significance to the disease or syndrome selected? Explain.

Identification of ENTM requires special laboratory equipment and techniques. This proposal will collect ENTM cases from sentinel sites, which will include any laboratory that can identify NTM outside of the lungs among Minnesota residents. This surveillance

will require all labs that have the capability to identify ENTM from a Minnesota resident to report to MDH. Laboratories statewide will be surveyed to fully assess which labs have the capability to identify NTM, and be required to report to MDH.

C. Did you consider the following factors? Explain.

a. Potential number of cases at the site

The incidence of ENTM in Minnesota is not well known; this is part of what we will learn through surveillance. MDH collected de-identified line list data from the four major reference laboratories that conduct laboratory testing and identification of NTM for the state. From 2013 to 2017, an estimated 490 cases of ENTM were diagnosed in Minnesota residents. We estimate that approximately 100 cases of ENTM will be diagnosed per year among Minnesota residents. However, as the data provided was de-identified, we believe this number could be an over-estimate of the true disease burden of ENTM in Minnesota.

b. Geographical distribution of cases or potential cases in Minnesota, if indicated by the epidemiology of the disease or syndrome

The geographic epidemiology of ENTM in Minnesota is relatively unknown; this is something we aim to assess with sentinel surveillance and data collection. By utilizing case data from laboratories that are able to identify NTM and conducting chart reviews and interviews of ENTM patients, we will have accurate geographic data from patients throughout Minnesota to further understand the geographic distribution of cases.

c. Epidemiology of the disease or syndrome

Surveillance data from other U.S. regions, along with worldwide data, demonstrate that ENTM cases are increasing, but the specific cause is unknown. As stated above, whether the increase in cases is real or whether more cases are simply being recognized and diagnosed remains unclear due to a lack of surveillance for ENTM. Outbreaks of ENTM in a variety of health care settings have occurred throughout the globe causing serious morbidity. Many components of the epidemiology of ENTM still need to be defined and understood, before effective prevention and control measures can be developed.

d. Overall impact of sentinel surveillance on a site and the benefit to public health in conducting sentinel surveillance at the site

Very little is known about the epidemiology of ENTM in Minnesota, and national data are very limited as ENTM is only reportable in eight states. Establishing sentinel ENTM surveillance will allow MDH to assess ENTM burden and risk factors, as well as provide insight into the epidemiology of this disease in Minnesota. Surveillance data will also allow MDH to identify and respond to ENTM outbreaks and contribute to an improved national understanding of the disease. This surveillance will provide local

data on burden, trends and risk factors, along with data on NTM species, and their antibiotic susceptibilities, which will ultimately lead to a more effect treatment after diagnosis.

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