Abstract

Epidemiological data show a worldwide increase in nontuberculous mycobacteriosis. Although it has been partially attributed to the improvement of microbiological methodologies that has allowed a better recovery and identification of nontuberculous mycobacteria (NTM), it is generally accepted that there is a genuine incidence augmentation. The reasons of the increase are likely multifactorial, depending on the nature of the pathogen, the host, and their interaction. Mycobacteria from the Mycobacterium tuberculosis complex has been regarded as pathogenic and NTM as opportunistic and nontransmissible. Nevertheless, few differences have been found in either their phenotypic or genotypic characteristics. The phenomenon of M. tuberculosis adaptation to the human host may be taking place again in NTM as a consequence of human environmental alterations that facilitate the interaction with the pathogen. The current worsening of the immunological status of increasing numbers of individuals, a result of factors such as malnutrition (obesity and diabetes), population aging or the widespread use of immunosuppressive medication, may be allowing the rapid evolution and person-to-person transmission of NTM. It is likely that mycobacteriosis incidence will keep escalating. New measures should be taken to deal with these diseases, including their reportability and the implementation of strain genotyping that would shed light on the NTM dissemination routes from the environment or human hosts.

Keywords: Adaptation, environment interaction, immunosuppression, pathogen, transmission

Introduction

Forty years ago, <50 species were recognized as nontuberculous mycobacteria (NTM) and they were not considered epidemiologically important pathogens [Figure 1a], although occasionally were associated to diseases that affected several organs. Since then, both physicians and researchers have been aware of the escalating incidence of pulmonary mycobacterial diseases, and several reviews, frequently updated, have addressed their worldwide epidemiology.[2‑5] Here, we discuss the potential explanations for this trend.

The Pathogen

Nearly 200 species of mycobacteria have been recognized (http://www.bacterio.net/mycobacterium.html) and NTM includes species other than Mycobacterium leprae, Mycobacterium lepromatosis, and the Mycobacterium tuberculosis complex.[1] They are ubiquitously distributed in the environment and have an extraordinary capacity to adapt and survive under adverse conditions, including nutrient deprivation and hypoxia.[6] The origin of pathogenic mycobacteria ancestors is not well known, but the example of M. tuberculosis complex may provide useful insights. Before becoming pathogenic, mycobacteria were likely environmental, as independent aquatic microorganisms.[7] A recent hypothesis suggests that the use of fire by humans was the trigger point because it promoted closer social interactions and incited pulmonary chronic inflammation by biomass smoke constituents.[8] Another hypothesis proposes a previous adaptation of mycobacteria to the Pleistocene megafauna.[9]

Little work has been done to address virulence factors in NTM but they have been thoroughly analyzed in M. tuberculosis, and the search of similarities between both...
may be informative. Virulence determinants of *M. tuberculosis* include proteins transported by the Type Seven Secretion System (T7SS). *M. tuberculosis* contains five T7SS, also called ESAT6 secretion system (ESX), and two members, ESX-1 and ESX-5, have been shown to be involved in virulence. ESX-1 is needed for phagosomal rupture and *Mycobacterium bovis* bacille Calmette–Guérin (BCG) does not gain access to the cytosol because it has lost a chromosomal fragment, the RD1 region that encodes for several genes of the ESX-1 system.10] Nevertheless, other pathogenic *M. tuberculosis* complex members have also the RD1 deletion, including *Mycobacterium microti*, *Mycobacterium mungi*, *Mycobacterium suricatti*, and the dassie bacillus.13] And other NTM, such as *Mycobacterium marinum*, *Mycobacterium fortuitum*, or *Mycobacterium komossi*, express ESX-1.12,13] In a recent report, 41 NTM species have been characterized by whole genome sequencing.14] They compared the genes of the Mce family that codify for secreted or cell envelope proteins, and that confers mycobacteria the ability to enter into mammalian cells.15] The genes belonging to Mce1, Mce2, Mce3, and Mce4 are present in *M. tuberculosis* and in many NTM species, while Mce5, Mce6, Mce7, Mce8, and Mce9 are present in most NTM species but absent in *M. tuberculosis*.14] In addition, mycobacteria have two SecA proteins, SecA1 and accessory SecA2 and SecA2 is essential for the full virulence of *M. tuberculosis*15] but the Sec system is conserved in all the species.14] Consequently, it seems that NTM share many of the *M. tuberculosis* virulence genes, but bioinformatics analysis has revealed that the phylogenetical distinction between pathogenic and nonpathogenic mycobacteria16] may be more relevant than between the *M. tuberculosis* complex and NTM.

**The Host**

As in any other infectious disease, the genetic variation of the host, originated by mutation, plays a fundamental role in the susceptibility to NTM. A majority of new mutations (mainly single nucleotide polymorphisms [SNPs]) are thought to have no effect and are deemed selectively neutral, but a few extreme deleterious mutations are lethal. Between both ends lay those variants that provide the genetic substrate for evolutionary change in response to infection.17] The nontuberculous mycobacteriosis in highly susceptible people is classified as Mendelian susceptibility to mycobacterial disease (MSMD)18] and is characterized by isolated infections with mycobacteria or *Salmonella* (also intracellular bacteria) due to a defect in the type-1 cytokine response. MSMD are frequently pediatric disorders and involve mutations in genes including *IL12B*, *IL12RB1*, *IFNGR1*, *IFNGR2*, *STAT1*, *IKBKG*, *CYBB*, *TYK2*, *IRF8*, and *ISG15* that cause either insufficient production of interferon γ or response to the cytokine. Strikingly, the incidence of tuberculosis in MSMD patients is relatively low, likely because early death precludes the diagnosis of these immunological defects.19]

Search of SNPs that cause susceptibility to *M. tuberculosis* has yielded few results, despite being the most studied infectious disease. In a recent systematic review, only SNPs in *IL4*, *TLR2*, and *CCL2* were reproducibly found as influential on the susceptibility to the disease20] although many other SNPs have been identified in genome-wide association studies (GWAS).21] In post-GWAS analysis, six intronic SNPs were found associated to tuberculosis susceptibility, located in *MARCO*, *IFNGR2*, *ASHAS2*, *ACACA*, *NISCH*, and *TLR2*.22] Regarding susceptibility to NTM, no GWAS have been conducted so far, but these studies may be very difficult to perform for these bacteria. An important problem with this approaches such as GWAS or linkage studies is that most infectious disease susceptibility genes have too small effect sizes and/or too low a frequency to allow being detected in even hundreds of families23].

**Interaction of the Host and Pathogen with the Environment**

Exposure to the NTM does not imply that the infected individual will develop an active disease. Dirac et al. have...
postulated two models of disease acquisition. The “susceptible person” model suggests that individuals will become sick regardless of the level of exposure to the mycobacteria, whereas the “unusual dose” model states that when individuals receive an unusually high dose of bacteria will develop the disease regardless of their immune status,[24] but they do not exclude each other. Susceptible individuals are exposed to larger doses of mycobacteria because they can grow on low levels of nutrients and have the ability to form biofilms which promotes their survival and dissemination on engineered habitats such as drinking water distribution systems, hospital water systems, and household plumbing that, nowadays, represent the most important sources of NTM.[25]

Tuberculosis incidence is declining,[26] and in some places, higher rates for nontuberculous mycobacterial disease have been reported.[27,28] NTM such as *Mycobacterium vaccae* has been used as immunotherapy for tuberculosis,[29] and a similar immunological cross-reaction may protect *M. tuberculosis* infected individuals from NTM. Consequently, less exposure to *M. tuberculosis* may cause increased NTM infections. Furthermore, *M. bovis* BCG has also been suggested to offer some immunity and countries that have halted vaccination campaigns have suffered higher incidence rates of nontuberculous mycobacterial diseases.[30,31]

**Changes in Factors that Affect the Epidemiology of Nontuberculous Mycobacteria**

**Progress in microbiological methodology**

Researchers have been puzzled on an increased number of reports of NTM infections in the last decades. An early explanation was that technical improvements in the isolation and identification of mycobacteria prompted a wider recognition of NTM as relevant pathogens. The use of fluorescence microscopy, culture in broth-based systems, and the development of rapid methods for identification, including polymerase chain reaction-restriction enzyme assay or high-performance liquid chromatography,[32] have allowed a better recovery and characterization of mycobacteria in clinical laboratories. Some authors believe that these improvements are behind the recognized increase in nontuberculous mycobacterial disease.[33] but others think that they are not the only reason.[34,35] In an interesting example, NTM isolation in Ontario in 2007,[36] Anthonisen assessed the possible reasons for the increased isolation. He remarked that there were no changes in isolation techniques at that time. He also ruled out general awareness by physicians because an increase in the number of cultures requested would have also implied a higher number of negative cultures that were not detected.[35] Some authors have reached the conclusion that technical progress contributes but does not justify the observed changes in incidence.[38,37]

**Changes in the host**

A microorganism may emerge as a pathogen because of changes in host susceptibility to infection. Important factors that will influence are the numeric increase in immunocompromised patients, aging of the population, and malnutrition[38] [Figure 1b]. Unlike diseases such as cancer that frequently arises from somatic mutations, hereditary diseases such as MSDS are supposed to be constant in the population.[38] Acquired immunodeficiencies also contribute to the number of patients with NTM. The most compelling example is the human immunodeficiency virus, commonly linked to mycobacteriosis. Nevertheless, the application of highly active antiretroviral therapy has reduced the rates of these infections.[39] Other acquired immunodeficiencies are those induced by anti-cytokine autoantibodies, especially against interferon γ and granulocyte macrophage colony-stimulating factor, more frequently associated to nontuberculous mycobacterial disease than to tuberculosis,[40] but their current epidemiological importance is unknown. In addition, immunosuppression induced by medical treatments for oncologic, rheumatologic, and neurologic disorders is increasing[38] and is a major cause of concern for nontuberculous mycobacteriosis. The use of tumor necrosis factor-α inhibitors such as etanercept, infliximab, or adalimumab increases the risk of tuberculosis 4–10 fold, but also of nontuberculous mycobacterial disease.[41] Furthermore, the incidence of autoimmune diseases is increasing in developed countries,[42] and several other immunosuppressive agents used for their treatment such as corticosteroids, leflunomide or hydroxychloroquine also increase the risk.[43]

Aging is another factor that affects the susceptibility, probably linked to the immunosenescence phenomenon. Prevalence is highest in people aged over 65. Given that elderly population is increasing, it is projected that epidemiology of NTM will remarkably change in the next few years. NTM infections in some elderly present particular features, such as those in the Lady Windermere syndrome, which is characteristic of older age females with no history of smoking.[44]

A last important factor in host susceptibility is malnutrition. The biological basis of poor nutritional status as a risk factor for tuberculosis has been well defined.[45] Malnutrition[46] and eating disorders[47] has been associated to nontuberculous mycobacterial disease. Although tuberculosis in the obese population is lower than in the nonobese population,[48] obesity increases the tendency to diabetes, which is known as an independent factor of active tuberculosis.[49] Although there is little information relative to the importance of diabetes for nontuberculous mycobacterial disease, it may be expected that it has a negative influence.[50]

**Changes in the pathogen**

Although *M. tuberculosis* strains have been isolated from the environment,[51] and compelling evidence suggest that *M. leprae* may survive outside their hosts,[52] mycobacteria from the *M. tuberculosis* complex and *M. leprae* are considered obligate pathogens, whereas NTM are viewed as opportunistic and their source is supposed to be exclusively the environment.[53] Human-to-human has not been considered a major route of transmission for NTM. A recent study using
whole genome sequencing of Mycobacterium abscessus isolates from cystic fibrosis patients identified multiple clades of near-identical isolates from geographically diverse locations. The authors suggested widespread transmission within the global cystic fibrosis community. Moreover, earlier reports also suggested the person-to-person transmission of Mycobacterium kansasii. To consider NTM as an airborne pathogen, it should follow the steps proposed by Herfst et al. First, association of the pathogen to aerosols or dust particles; second, deposition of the pathogen in the recipient, usually by inhalation; third, amplification of the pathogen, either in the respiratory tract or in peripheral tissues; and fourth, its emergence at the site of shedding (frequently the upper respiratory tract) in sufficient loads and capable of expulsion. The frequent detection of acid-fast bacilli in sputum suggests that the first and second steps are easily accomplished by NTM. The reason for the difficulties of transmission will probably lie in the third step because an appropriate immune response will impair the amplification of the pathogen. If the immune response is no longer successful, NTM may become transmissible [Figure 1c]. Additional evidence that supports the transmissibility of NTM has been addressed in a Caenorhabditis elegans model, and it has been confirmed that Mycobacterium avium shed by a host through the digestive route is able to infect a new one.

The impression that most NTM are mostly colonizers may also be changing. Since some mycobacteria were recognized as relevant pathogens, they have all been perceived as potentially pathogenic. Human macrophages infected in vitro with Mycobacterium gordonae, frequently regarded as a nonpathogenic mycobacterium, or with M. tuberculosis, are unable to restrict the intracellular multiplication of the mycobacteria, suggesting that M. gordonae share with M. tuberculosis some of the means to resist destruction by macrophages. Many mycobacteria have been reported in one or more clinical cases, although erroneous identification remains an important problem.

Mutator microorganisms, with an increased rate of spontaneous mutations resulting from defects in DNA repair or error avoidance systems, can become resistant to antibiotics, evolve to a higher level of virulence, and acquire persistence or transmissibility. NTM may take advantage from positive selection of mutators to survive in the environment and to invade humans. Although the first evidence for a specific environment driving the selection of hypermutable strains was obtained in a study of Pseudomonas aeruginosa in cystic fibrosis patients, mycobacteria also seem to share a mutator phenotype. A remarkable example is the single natural nucleotide mutation that is able to convert a human-specific Staphylococcus aureus strain into one that can infect rabbits. NTM may be already following this path to enhance virulence in immunocompromised chronically infected individuals [Figure 1c]. Twenty years ago, NTM isolates were considered unimportant in patients with cystic fibrosis; but in the last few decades, a few clones have been able to spread widely within this population, and they share several pathogenic features that suggest the establishment of transmission chains that may have permitted M. abscessus to evolve from an environmental organism to a true human lung pathogen. This adaptation to the human host is worrying because it may have taken place in a few years. Another example is M. kansasii which has been classified into seven subtypes. Strains from the subtype 1 are the most common in humans suggesting that they are better adapted to the host. In addition, a study in Australia showed that very few strains of M. kansasii obtained from municipal waters were similar or related to clinical isolates, possibly indicating that isolates from humans have become different from their environmental counterparts.

CONCLUDING REMARKS

If the incidence and prevalence of the disease continue to increase, the problem of drug-resistant NTM will become bigger than tuberculosis, and we need to take action now against the worldwide nontuberculous mycobacterial disease epidemic. An appropriate measure is to make it a reportable disease to public health authorities. The benefits of reporting extrapulmonary nontuberculous mycobacterial disease are evident because most of the times, they represent true disease and could come from contaminated surgical, cosmetic, or other procedures that public health action may prevent. The reasons for reporting pulmonary NTM are more difficult to justify because frequently, they are not associated to disease. Nevertheless, reporting can improve our knowledge on the current situation of nontuberculous mycobacterial epidemic and allow us to build up a capacity for diagnosis and treatment at local and international levels.

Mycobacterial genotyping is an additional measure that will help the identification of environmental strains that may have already taken the path of adaptation to the human host. Genotyping systems are well developed for the M. tuberculosis complex. In contrast, comparatively fewer efforts have been performed in NTM. Several objectives will be accomplished by genotyping, including the identification of virulent strains for risk analysis, strain tracking to identify source of exposure, and description of population structures and forces acting on them. Nowadays, next-generation sequencing will be the methodology of election, but given the large number of NTM species and their lower virulence, it seems unlikely that its use will become widespread. Simpler and more cost-effective alternatives would be more appropriate. These diseases deserve to be taken rather seriously and further research should help us dealing with their emergent nature. It may be safely predicted that their incidence will keep escalating.

Acknowledgments

Dr. Rivero-Lezcano is a member of the Fundación Instituto Ciencias de la Salud de Castilla y León and participates in the SACYL Research Programme. González-Cortés was supported by a grant from Ministerio de Economía
y Competitividad, subprogram of technical support staff, 2015 (PTA2015-11248-I).

**Financial support and sponsorship**

This work was supported by Consejería de Sanidad de la Junta de Castilla y León GRS 1225/A/16 and by Sociedad Española de Neumología y Cirugía Torácica (SEPAR) (204/2015).

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Wolinsky E. Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 1979;119:107-59.
2. Kee SJ, Suh SP. Increasing burden of nontuberculous mycobacteria in Korea. J Korean Med Sci 2017;32:1215-6.
3. Stout JE, Koh JW, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. Int J Infect Dis 2016;45:123-34.
4. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: A review. Clin Chest Med 2015;36:13-34.
5. Wassilew N, Hoffmann H, Andrejak C, Lange C. Pulmonary disease caused by non-tuberculous mycobacteria. Respiration 2016;91:386-402.
6. Cook GM, Berney M, Gebhard S, Heinemann M, Cox RA, Danilchanka O, et al. Physiology of mycobacteria. Adv Microb Physiol 2000;55:81-182, 318-9.
7. Djelouadji Z, RaoulD, Drancourt M. Palaeogenomics of Mycobacterium tuberculosis: Epidemic bursts with a degrading genome. Lancet Infect Dis 2011;11:641-50.
8. Chisholm RH, Trauer JM, Curnoe D, Tanaka MM. Controlled fire use and proteomic analysis of four non-tuberculous mycobacterial infection. PLoS Pathog 2010;6:e1000895.
9. Orgeur M, Brosch R. Evolution of virulence in the Mycobacterium tuberculosis complex. Curr Opin Microbiol 2018;41:68‑75.
10. Abdallah AM, Gey van Pittius NC, Champion PA, Cox J, Luirink J; et al. Comparative genomics and proteomic analysis of four non-tuberculous mycobacterial disease, Japan (1). Emerg Infect Dis 2016;22:1116‑7.
11. Marras TK, Daley CL. Epidemiology of human pulmonary infection with nontuberculous mycobacteria. Clin Chest Med 2002;23:556‑7.
12. Carlsson F, Kim J, Dumitru C, Barck KH, Carano RA, Sun M, et al. The role of host genetic factors in respiratory tract infectious disease susceptibility. Philos Trans R Soc Lond B Biol Sci 2012;367:840‑9.
13. Dirac MA, Horan KL, Doody DR, Meschke JS, Park DR, Jackson LA, et al. Environment or host?: A case-control study of risk factors for Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2012;186:684‑91.
14. Falkinham JO 3rd. Surrounded by mycobacteria: Nontuberculous mycobacteria in the human environment. J Appl Microbiol 2009;107:356‑67.
15. Morbidity and mortality: A review. Clin Chest Med 2015;36:13-34.
16. Sullivan JS, Schaffner W, McCarthy DJ, et al. Nontuberculous mycobacteria in the human environment. J Appl Microbiol 2015;117:663‑72.
17. The role of host genetic factors in respiratory tract infectious disease susceptibility. Philos Trans R Soc Lond B Biol Sci 2012;367:840‑9.
18. Dirac MA, Horan KL, Doody DR, Meschke JS, Park DR, Jackson LA, et al. Environment or host?: A case-control study of risk factors for Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2012;186:684‑91.
19. Falkinham JO 3rd. Surrounded by mycobacteria: Nontuberculous mycobacteria in the human environment. J Appl Microbiol 2009;107:356‑67.
20. Sullivan JS, Schaffner W, McCarthy DJ, et al. Nontuberculous mycobacteria in the human environment. J Appl Microbiol 2015;117:663‑72.
21. Morbidity and mortality: A review. Clin Chest Med 2015;36:13-34.
Rivero-Lezcano, et al.: Increasing nontuberculous mycobacteriosis

Eur J Intern Med 2014;25:356-63.
45. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: Evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 2004;8:286-98.
46. Ikegame S, Maki S, Wakamatsu K, Nagata N, Kumazoe H, Fujita M, et al. Nutritional assessment in patients with pulmonary nontuberculous mycobacteriosis. Intern Med 2011;50:2541-6.
47. Portillo K, Morera J. Nutritional status and eating disorders: Neglected risks factor for nontuberculous mycobacterial lung disease? Med Hypotheses 2012;78:39-41.
48. Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol 2010;39:149-55.
49. Odone A, Houben RM, White RG, Lönnroth K. The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets. Lancet Diabetes Endocrinol 2015;2:754-64.
50. Bridson T, Govan B, Keteehan N, Norton R. Overrepresentation of diabetes in soft tissue nontuberculous mycobacterial infections. Am J Trop Med Hyg 2016;95:528-30.
51. Velayati AA, Rahideh S, Nezhad ZD, Farnia P, Mirsaeidi M. Nontuberculous mycobacterium in Middle East: Current situation and future challenges. Int J Mycobacteriol 2015;4:7-17.
52. Franco-Paredes C, Rodriguez-Morales AJ. Unsolved matters in leprosy: A descriptive review and call for further research. Ann Clin Microbiol Antimicrob 2016;15:33.
53. Halstrom S, Price P, Thomson R. Review: Environmental mycobacteria as a cause of human infection. Int J Mycobacteriol 2015;4:81-91.
54. Bryant JM, Grogono DM, Rodriguez-Rincon D, Everall I, Brown KP, Moreno P, et al. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous Mycobacterium. Science 2016;354:751-7.
55. Penny ME, Cole RB, Gray J. Two cases of Mycobacterium kansasii infection occurring in the same household. Tubercle 1982;63:129-31.
56. Lichtenstein MR, Takimura Y, Thompson JR. Photochromogenic mycobacterial pulmonary infection in a group of hospitalized patients in Chicago. II. Demographic studies. Am Rev Respir Dis 1965;91:592-5.
57. Ricketts WM, O’Shaughnessy TC, van Ingen J. Human-to-human transmission of Mycobacterium kansasii or victims of a shared source? Eur Respir J 2014;44:1085-7.
58. Herbst S, Böhringer M, Kao B, Lawrence P, Lewis NS, Mina MJ, et al. Drone of airborne human-to-human pathogen transmission. Curr Opin Virol 2017;22:22-9.
59. Bermudez LE, Rose SJ, Everman JL, Ziaie NR. Establishment of a host-to-host transmission model for Mycobacterium avium subsp. Hominis using Caenorhabditis elegans and identification of colonization-associated genes. Front Cell Infect Microbiol 2018;8:123.
60. Wayne LG, Sramek HA. Agents of newly recognized or infrequently encountered mycobacterial diseases. Clin Microbiol Rev 1992;5:1-25.
61. Reyes-Ruvalcaba D, González-Cortés C, Rivero-Lezcano OM. Human phagocytes lack the ability to kill Mycobacterium gordoneae, a non-pathogenic mycobacteria. Immunol Let 2008;116:72-8.
62. Jiménez MS, Julián E, Luquin M. Misdiagnosis of Mycobacterium brumae infection. J Clin Microbiol 2011;49:1190-1.
63. Oliver A. Mutators in cystic fibrosis chronic lung infection: Prevalence, mechanisms, and consequences for antimicrobial therapy. Int J Med Microbiol 2010;300:563-72.
64. Oliver A, Cantón R, Campo P, Baquero F, Blázquez J. High frequency of hypermutable Pseudomonas aeruginosa in cystic fibrosis lung infection. Science 2000;288:1251-4.
65. Castañeda-Garcia A, Prieto AI, Rodriguez-Beltrán J, Alonso N, Cantillon D, Costas C, et al. A non-canonical mismatch repair pathway in prokaryotes. Nat Commun 2017;8:14246.
66. Viana D, Comos M, McAdam PR, Ward MJ, Selva L, Guinane CM, et al. A single natural nucleotide mutation alters bacterial pathogen host tropism. Nat Genet 2015;47:361-6.
67. Torrens JK, Dawkins P, Conway SP, Moya E. Non-tuberculous mycobacteria in cystic fibrosis. Thorax 1998;53:182-5.
68. Alcaide F, Richter I, Bernasconi C, Springer B, Hagenau C, Schulze-Röbbecke R, et al. Heterogeneity and clonality among isolates of Mycobacterium kansasii: Implications for epidemiological and pathogenicity studies. J Clin Microbiol 1997;35:1959-64.
69. Thomson R, Tolson C, Huygens F, Hargreaves M. Strain variation amongst clinical and potable water isolates of M. kansasii using automated repetitive unit PCR. Int J Med Microbiol 2014;304:484-9.
70. McGrath EE, Anderson PB. Increased prevalence of non-tuberculous mycobacteria infection. Lancet 2007;370:28.
71. Isemann MD, Marras TK. The importance of nontuberculous mycobacterial lung disease. Am J Respir Crit Care Med 2008;178:999-1000.
72. Winthrop KL, Henkle E, Walker A, Cassidy K, Hedberg K, Schafer S, et al. On the reportability of nontuberculous mycobacterial disease to public health authorities. Am Am Thorac Soc 2017;14:314-7.
73. Ei PW, Aung WW, Lee JS, Choi GE, Chang CL. Molecular strain typing of Mycobacterium tuberculosis: A review of frequently used methods. J Korean Med Sci 2016;31:1673-83.
74. Behr MA, Falkingham JO 3rd. Molecular epidemiology of nontuberculous mycobacteria. Future Microbiol 2009;4:1009-20.