

Epidemiology of Pulmonary Nontuberculous Mycobacterial Disease, Japan¹

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DOI: <http://dx.doi.org/10.3201/eid2206.151086>

To the Editor: Incidence of pulmonary nontuberculous mycobacterial disease (PNTMD) is reportedly increasing globally (1,2). Although such an increase is expected in Japan (3,4), the epidemiologic situation is unclear. The most recent survey, which used the 1997 American Thoracic Society diagnostic criteria, reported that the incidence rate for PNTMD in 2007 was 5.7 cases per 100,000 person-years (5). To update the data, we performed a nationwide hospital-based survey in Japan.

After a preliminary survey of 20 hospitals, we developed and disseminated questionnaires to all 884 hospitals in Japan that were certified by the Japanese Respiratory Society. The surveys asked about the number of newly diagnosed cases, from January through March 2014, of PNTMD, pulmonary *Mycobacterium avium* disease, *M. intracellulare* disease, or *M. avium* complex (MAC; the combination of the first 2 species listed); pulmonary *M. kansasii* disease; pulmonary *M. abscessus* disease; and tuberculosis (TB) for inpatients and outpatients. Hospital respondents returned the completed questionnaires by mail, fax, or Internet. To avoid potential reporting bias and misclassification, we counted only cases that met the 2007 American Thoracic Society/Infectious Diseases Society of America statements (6) and excluded cases diagnosed at other hospitals. Because the source population can be ascertained by using the epidemiologic data for TB as a reportable disease, to estimate the incidence rate of PNTMD, we used the ratio of TB to PNTMD cases. The PNTMD incidence rate was calculated as the national incidence rate of TB

multiplied by the ratio of new PNTMD to TB cases reported by the responding hospitals (online Technical Appendix Figure 1, <http://wwwnc.cdc.gov/EID/article/22/6/15-1086-Techapp1.pdf>).

To clarify the chronologic changes in incidence, we followed the same method for comparing TB and PNTMD used in a prior epidemiologic study in Japan (5). We established methods for maximizing survey response rates and facilitating ease of completion by offering extensive support to survey recipients (online Technical Appendix Table 1).

We achieved a high response rate of 62.3% (551 hospitals), and in all regions the response rate exceeded 50% (online Technical Appendix Table 2). The numbers of newly diagnosed cases were 2,327 for TB and 2,652 for PNTMD. Because the incidence rate for TB was reported to be 12.9 cases per 100,000 person-years, that of PNTMD was estimated to be 14.7 cases per 100,000 person-years, which is ≈ 2.6 times the incidence rate reported in 2007 (Figure). By using the same method, we found the incidence of pulmonary MAC, *M. kansasii*, and *M. abscessus* disease to be 13.1, 0.6, and 0.5 cases per 100,000 person-years, respectively (online Technical Appendix Table 2). The ratio of pulmonary *M. avium* disease to MAC was higher in the northern and eastern parts of Japan, whereas the ratio of pulmonary *M. intracellulare* disease to MAC was higher in the southern and western parts of Japan (online Technical Appendix Figure 1).

From this survey, we observed that the incidence rate of PNTMD may exceed that of TB and that incidence rates of PNTMD in Japan may be among the highest worldwide (Figure). This finding implies that the prevalence of PNTMD as a chronic infection is estimated to be much higher than that of TB.

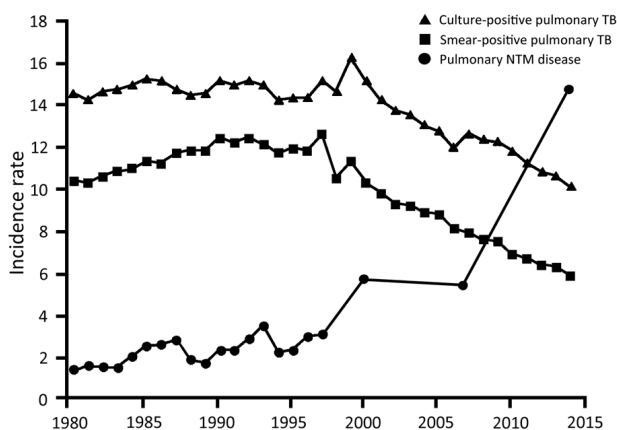


Figure. Incidence (no. cases/100,000 person-years) of pulmonary nontuberculous mycobacterial (NTM) disease, culture-positive tuberculosis (TB), and smear-positive TB in Japan during 1980–2014. The nationwide survey revealed that the incidence rate of pulmonary NTM disease exceeds that of TB. The epidemiologic survey before 1988 was conducted annually by the same research group; subsequently, another group performed the epidemiologic survey only in 2001 and 2007.

¹Preliminary results from this study were presented at the American Thoracic Society 2015 International Conference; 2015 May 15–20; Denver, Colorado, USA (http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A5268).

We assume that the high rates of PNTMD in Japan are consistent with data suggesting that Asians are particularly susceptible to PNTMD (1,7,8). Other factors contributing to the increase might be the simplified diagnosis according to the 2007 American Thoracic Society/Infectious Diseases Society of America statements, increased awareness by medical staff, population aging, and increased frequency of medical checkups with computed tomography of the chest.

Another finding was the characteristic gradient clustering of the ratios of *M. avium* and *M. intracellulare* (online Technical Appendix Figure 2). This finding supports the widely accepted belief that environmental factors strongly affect the epidemiology of PNTMD; therefore, the role of factors such as soil, humidity, temperature, and saturated vapor pressure should be seriously considered (9).

We also found dramatic increases in incidence of pulmonary *M. abscessus* disease and pulmonary MAC disease, whereas incidence of pulmonary *M. kansasii* disease was stable. Although we did not distinguish *M. massiliense* from *M. abscessus*, the incidence rate for pulmonary *M. abscessus* disease increased from 0.1 cases in 2001 to 0.5 cases per 100,000 person-years in 2014. This epidemiologic tendency should be monitored (10).

This study has several limitations. First, differing characteristics between the responding and nonresponding hospitals could cause bias. Second, we did not collect data outside of hospitals. Third, incomplete reporting could undermine the accuracy of our estimates (online Technical Appendix Tables 3, 4). Therefore, the epidemiologic data should be verified by using other approaches (online Technical Appendix Table 1).

The dramatic increase in incidence rates for PNTMD warrants its recognition as a major public health concern. Because the prevalence rates of this currently incurable lifelong chronic disease are estimated to be high, the effect on the community could be enormous. Further investigations are needed.

This research was supported by the Research Program on Emerging and Re-emerging Infectious Disease from the Japan Agency for Medical Research and Development. The nationwide survey was also supported by the Japanese Respiratory Society; the Japanese Society for Tuberculosis; and the Ministry of Health, Labour and Welfare.

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Elevated Pertussis Reporting in Response to 2011–2012 Outbreak, New York City, New York, USA

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DOI: <http://dx.doi.org/10.3201/eid2206.151514>

To the Editor: Pertussis is a highly communicable, acute bacterial respiratory infection caused by *Bordetella pertussis*. In the United States, the incidence of pertussis declined dramatically after pertussis-containing vaccine was introduced in the 1940s (1,2). However, a resurgence

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Technical Appendix

Technical Appendix Table 1. Characteristics of this nationwide survey and other approaches for estimating the epidemiological data of PNTMD*

Multidisciplinary approaches for the accuracy of the epidemiological data in this nationwide survey*

| | |
|---|--|
| A | We conducted a preliminary survey of 20 hospitals before this survey. The aim of this preliminary survey was to identify points for improvement in the survey methods. We have discussed these points with the responders, and have modified the questionnaire contents to enhance understandability. |
| B | We strongly advised the responders to calculate the cases of newly diagnosed PNTMD by referring to an in-house bacteriological laboratory or external laboratory company because cases must be diagnosed in accordance with the 2007 ATS/IDSA statements. Specifically, the responders were advised to inquire about cases with respiratory specimens that are positive for NTM during the study period. Subsequently, they confirmed that these cases met the diagnostic criteria for the first time during the study period. |
| C | As another way to calculate the number of PNTMD, we recommended the use of the ICD-10 system. Under the Japanese health insurance system, an ICD-10 code should be assigned and the date of diagnosis should be documented in a patient's medical chart. We encouraged responders to use their own hospital's ICD-10 database to find newly diagnosed PNTMD during the study period. |
| D | To ensure adequate understanding of the responders, we disseminated this information through a Frequently Asked Questions document. We created a website for this survey to obtain precise information easily. We requested them to provide their e-mail addresses and phone numbers, and we directly contacted the responder if the data appeared doubtful. |
| E | The government (Ministry of Health, Labour and Welfare), the Japanese Respiratory Society, and the Japanese Society for Tuberculosis sent official documents requiring accurate Japanese epidemiological data to each hospital. These actions may have partially contributed to increasing the accuracy of our data. |

Other approaches for estimating the epidemiological data of PNTMD

| | |
|---|---|
| A | Surveillance from laboratories that performed mycobacterial cultures. |
| B | Use of electrical medical records on PNTMD. |
| C | Utilization of postmarketing surveillance of antimycobacterial drugs. |

*PNTMD: pulmonary nontuberculous mycobacterial disease; ATS/IDSA: American Thoracic Society/Infectious Diseases Society of America; ICD: International Classification of Diseases.

Technical Appendix Table 2. Response rate and results of survey of newly diagnosed pulmonary nontuberculous mycobacterial disease and mycobacterial disease, January–March 2014, Japan*

| Region | Hospitals, no. | Response rate, % | <i>M.</i> | | | | | | | TB |
|------------|-------------------|---------------------|-----------|-----------------|-----------------------|-----|-----------------|------------------|--------|-------|
| | | | NTM | <i>M. avium</i> | <i>intracellulare</i> | MAC | <i>kansasii</i> | <i>abscessus</i> | Others | |
| Hokkaido | 34 | 58.8 | 74 | 48 | 6 | 12 | 3 | 1 | 4 | 45 |
| Tohoku | 61 | 55.7 | 147 | 101 | 33 | 5 | 2 | 2 | 4 | 58 |
| Kanto | 262 | 69.5 | 1,010 | 568 | 174 | 159 | 54 | 32 | 23 | 851 |
| Chubu | 145 | 58.6 | 435 | 257 | 115 | 25 | 5 | 13 | 20 | 400 |
| Kinki | 143 | 58.0 | 498 | 262 | 149 | 10 | 35 | 25 | 17 | 511 |
| Chugoku | 61 | 60.7 | 159 | 88 | 51 | 5 | 4 | 3 | 8 | 138 |
| Shikoku | 41 | 51.2 | 69 | 26 | 25 | 12 | 0 | 5 | 1 | 78 |
| Kyushu | 124 | 63.7 | 239 | 77 | 114 | 15 | 10 | 6 | 17 | 218 |
| Okinawa | 13 | 76.9 | 21 | 6 | 12 | 0 | 0 | 1 | 2 | 28 |
| Nationwide | 884 | 62.3 | 2,652 | 1,433 | 679 | 243 | 113 | 88 | 96 | 2,327 |

M., *Mycobacterium*, MAC: *Mycobacterium avium* complex. NTM, nontuberculous mycobacteria; TB, tuberculosis.

Technical Appendix Table 3. Limitations of this nationwide survey*

| Study limitations | |
|-------------------|---|
| A | Any differences of characteristics between the responding and nonresponding hospitals could cause a bias because the calculation method adopted in this study was based on the assumption that the ratio of PNTMD to tuberculosis is the same between these two groups. However, the apparent differences between the two groups were not admitted in terms of the number of beds, type of hospital (public vs. private), and whether the hospital is teaching or nonteaching (Appendix Table 3). |
| B | We did not collect data on tuberculosis and PNTMD outside hospitals. Regarding tuberculosis, primary care physicians tend to send suspected cases to hospitals with respiratory physicians in general, mainly due to the relatively high probability of tuberculosis in Japan. On the other hand, because of more complicated diagnostic criteria, we assume that a certain number of PNTM cases could be undiagnosed in the clinics since additional results of cultures may not be confirmed. |
| C | Incomplete reporting could undermine the accuracy of our estimate. |

*PNTMD: pulmonary nontuberculous mycobacterial disease.

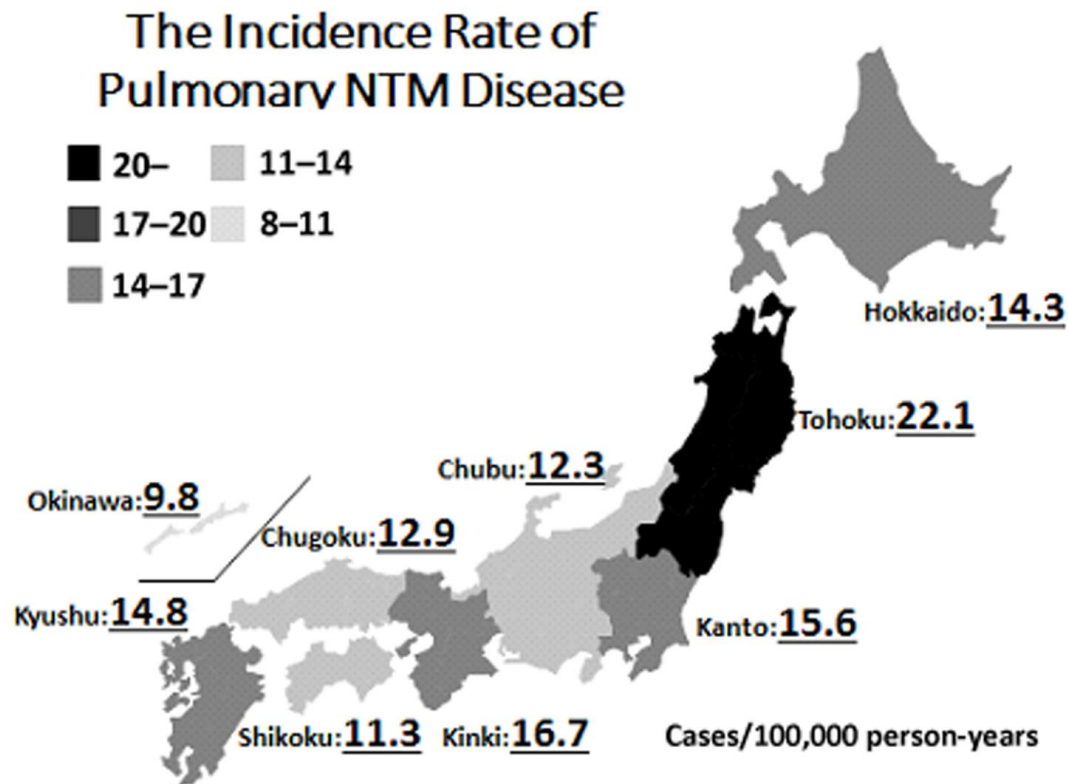
Technical Appendix Table 4. The comparison between responded hospitals and non-responded hospitals*

| Variable | Responding hospitals (n=551) | Nonresponding hospitals (n=333) | P value |
|---|---|--|--------------------|
| The number of beds mean \pm SD (range) | 409.5 \pm 239.0 | 402.5 \pm 226.3 | 0.178 [†] |
| Type of hospital, no(%) | Public 364 (66.1%) / Private 187 (33.9%) | Public 224 (67.3%)/ Private 109 (32.7%) | 0.713 [§] |
| Teaching hospital, no(%) | 404 (73.3%) | 261 (78.4%) | 0.092 [§] |

*SD: standard deviation

†: Student's t-test

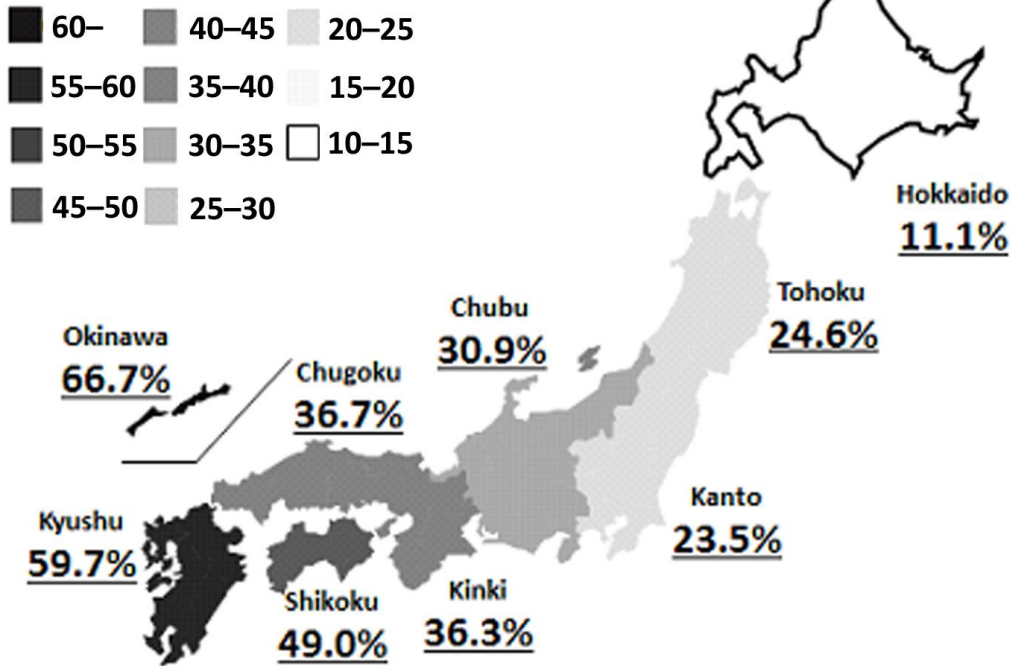
§: χ^2 test.



$$\begin{array}{c}
 \boxed{\text{Incidence rate of PNTM disease}} = \boxed{\text{Incidence rate of TB}} \times \frac{\boxed{\text{Newly diagnosed PNTM patients}}}{\boxed{\text{Newly diagnosed TB patients}}} \\
 \downarrow \qquad \qquad \qquad \downarrow \\
 \text{Reportable Disease} \qquad \text{Examined by the Survey}
 \end{array}$$

Technical Appendix Figure 1. The incidence rate of pulmonary NTM disease and pulmonary MAC disease are highest in Tohoku and lowest in Okinawa, the most southern part of Japan. The incidence rate of PNTMD was calculated as the national incidence rate of tuberculosis multiplied by the number of new PNTMD, divided by the number of new tuberculosis cases. NTM: Nontuberculous mycobacteria, PNTMD: Pulmonary nontuberculous mycobacterial disease.

M. avium vs *M. intracellualre*
(ratio of *M. intracellualre*)



Technical Appendix Figure 2. Incidence of pulmonary *Mycobacterium avium* disease is higher in the northern and eastern parts of Japan, while that of pulmonary *Mycobacterium intracellulare* disease is higher in the southern and western parts of Japan. These findings are similar to those reported in the 2007 survey.