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Nontuberculous mycobacterial infection in Wisconsin children and adolescents

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ABSTRACT

Background: The epidemiology of nontuberculous mycobacteria (NTM) infections in the pediatric population is not well described. We estimated the incidence of NTM infection in Wisconsin children and adolescents, and the frequency and type of infection caused by different NTM pathogens. Associations between NTM infection and race/ethnicity and social disadvantage, respectively, were also investigated.

Methods: This retrospective cohort study evaluated reports of NTM infection in Wisconsin residents under 18 years of age submitted to a state-wide database between 2011 and 2018. Demographics of the cohort, including a social disadvantage score (Area Deprivation Index (ADI)), are described. Specimen type and NTM species are enumerated for reported isolates.

Results: There were 224 NTM isolates from 212 children and adolescents. Median age of participants was 3 years; 55 % were female. Cumulative incidence did not vary significantly between the larger racial groups or for the various ADI score groups. Compared to white participants (157), there was a significantly lower cumulative incidence of NTM infection in multiracial individuals (2). *Mycobacterium avium* complex (MAC) was the most frequently isolated organism (69 %). The majority of isolates (52 %) were from skin and soft tissue, which included lymph node specimens. Annual incidence did not vary significantly over the study period.

Conclusions: The epidemiology of pediatric NTM infections in this cohort is consistent with previous pediatric reports of higher rate of infection in females and predominance of skin and soft tissue infections. Disparities in disease burden across racial/ethnic and socio-economic groups were not demonstrated, but these factors should be further explored in larger pediatric studies of diverse U.S. populations.

1. Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment, found in soil, natural bodies of water, and municipal water supplies [1]. NTM include all species of the genus *Mycobacterium* aside from members of the *M. tuberculosis* complex and the agents of Hansen's disease (leprosy). Over 190 unique NTM species and subspecies have been described [2]. A number of studies have reported an increase in the incidence or prevalence of NTM disease [3–11], while others report no significant changes over time [12–14]. Reported increases in NTM disease may result from improved detection of NTM species using molecular techniques, such as PCR and mass spectrometry, or increased screening. Alternately, changes in the geophysical environment, including water treatment [15], climate change, aging populations, or broader use of immunosuppressive drugs may drive a true increase in NTM incidence.

Comprehensive studies of NTM epidemiology in the pediatric population are lacking. In the pediatric population, NTM disease most often presents with skin and soft tissue infection or lymphadenitis [16]. Pulmonary infection is uncommon and tends to occur in patients with cystic

Abbreviations: ADI, Area Deprivation Index; CI, confidence interval; IQR, interquartile range; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria; WEDSS, Wisconsin Electronic Disease Surveillance System.

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fibrosis [17]. Disseminated disease is rare and confined to patients with primary immunodeficiency syndromes (e.g., molecular lesions in the IL-12 or interferon γ signaling pathways) [18] or acquired immunodeficiency (advanced HIV, use of tumor necrosis factor inhibitors, steroids, or other immunosuppressive drugs) [19]. The aim of this study was to estimate the incidence of NTM infection in Wisconsin children and adolescents (under 18 years of age) by race and social disadvantage and to characterize the frequency and type of infection caused by different NTM pathogens.

2. Methods

2.1. Study design

This retrospective cohort study used laboratory reports of all NTM isolates from Wisconsin residents less than 18 years of age submitted to the Wisconsin Electronic Disease Surveillance System (WEDSS) from 2011 to 2018.

2.2. Data collection

Wisconsin is one of a handful of states in which nontuberculous mycobacterial infection is notifiable and is reported to an electronic data repository, the Wisconsin Electronic Disease Surveillance System (WEDSS). Inputs to WEDSS include laboratory reports of mycobacterial cultures received from the Wisconsin State Laboratory of Hygiene (WSLH, approximately 40 % of all NTM isolates), other laboratories in Wisconsin (approximately 50 % of all NTM isolates), and national reference laboratories (approximately 10 % of isolates). Laboratory personnel at the facilities submitting samples extracted information from patients' medical records to complete requisition forms, including demographic data, that was then entered to WEDSS. No universal standard definition for the terms "race" or ethnicity" was applied. Clinical data are generally not captured for reports of NTM. For this study, data extracted from WEDSS included a unique case identification number, age, gender, race/ethnicity, street address, county of residence, date of specimen collection, specimen type (tissue site), mycobacterial species, and reporting laboratory. Reports from individuals living outside Wisconsin or of unknown age were excluded. Isolates of *M. gordonae* are generally considered non-pathogenic contaminants and were excluded. Identical species isolated from the same site within one year were enumerated as single infections. Multiple reports of infection from the same individual were included if (1) species were non-identical; (2) isolates were collected from different sites (for example, lung and skin); or (3) isolates were collected more than one year apart. Laboratory reports contain the type of specimen and the site or source of specimen collection at various degrees of granularity. Each specimen was categorized as from either a respiratory, non-respiratory or unspecified site. The non-respiratory category was further subcategorized into nine mutually exclusive subcategories (skin and soft tissue-neck, skin and soft tissue-head (non-neck), skin and soft tissue-extremity, skin and soft tissue-other, skin and soft tissue-unspecified, musculoskeletal, gastrointestinal, blood, or mediastinal). Skin and soft tissue subcategories include lymph node specimens. Given the absence of clinical data, cases of NTM "disease" were not defined in this study. Nonetheless, it is very likely that NTMs isolated from skin and soft tissue, lymph nodes, or normally sterile sites indicate disease rather than colonization. Respiratory specimens for mycobacterial culture were presumably collected from patients in whom NTM infection was possible or suspected. Thus, in this analysis, instances of NTM isolation were defined as cases of NTM infection.

Molecular assays used throughout most of the study period were unable to distinguish among *M. avium, M. chimaera,* and *M. intracellulare*. These three species were thus grouped together as "*Mycobacterium avium* complex (MAC)" in this analysis. Since laboratory methods in use before 2015 generally could not discriminate among the three *M. abscesses* subspecies (*M. abscessus abscess*, *M. abscessus bolletti*, and *M. abscessus massiliense*) and *M. chelonae*, these species and subspecies were grouped together as "*M. chelonae-abscessus* group."

2.3. Area Deprivation Index score

The Area Deprivation Index (ADI) score provides a comparative ranking of socio-economic status at the census block group level using street address as an input. ADI state rank scores of 1 (least disadvantaged) through 10 (most disadvantaged) were assigned to each individual in the database with home street address reported, using the online tool Neighborhood Atlas® [20,21]. Individual address data were removed after assignment of ADI score to de-identify the dataset.

2.4. Data analysis

Demographic features of study participants and NTM isolate characteristics were summarized by calculating proportions, medians, and interquartile ranges using the software program Stata version 16 (StataCorp, College Station, TX). Cumulative incidence of NTM infection (per 100,000 residents under 18 years of age) and their Poisson 95 % confidence intervals over the study period were calculated using population data from the American Community Survey [22]. For subjects with multiple episodes of NTM infection (defined above), demographic analyses utilized subject characteristics at the time of first reported NTM isolation. The cumulative incidence of individuals with NTM infection were compared across sex and racial/ethnic groups using Fisher's Exact Test. The frequency of individuals with NTM infection within each ADI state rank score was compared to the expected frequency using the chi-square goodness of fit test. Small case numbers in all but the white and non-Hispanic groups precluded stratified analysis of ADI data by race or ethnicity.

2.5. Ethical considerations

The study design and use of de-identified human data were approved by the Wisconsin Department of Health Services and the Institutional Review Board of the University of Wisconsin School of Medicine and Public Health.

3. Results

A total of 212 Wisconsin children and adolescents with NTM infection and 224 total NTM isolates were reported to the WEDSS database. There were 5 instances of co-infection and 7 instances of a second (subsequent) infection, all of which were from respiratory specimens. As shown in Table 1, there was a slight female predominance in the overall cohort (55.2 %). The median age for all study participants was 3 years; 138 (65.1 %) were five years of age or younger. The median age for 74 participants with respiratory infection was 13 years (interquartile range (IQR): 5 to 16 years). The median age for 128 participants with NTM skin and soft tissue infection (inclusive of lymph node specimens) was 2 years (IQR: 1 to 3 years).

Race/ethnicity was ascertained in 197 (92.9 %) individuals. Cumulative NTM incidence across racial groups was significantly different ($p < 0.05$), with multiracial individuals having significantly lower incidence (3.5 per 100,000) than white participants as the reference group, though this analysis notably included only two multiracial individuals. Asian participants had the highest incidence (23.8 per 100,000). Black participants had slightly higher rates of NTM isolation than white participants (19.7 and 14.6 per 100,000, respectively). Hispanic or Latinx ethnicity was ascertained in 198 (93.4 %) individuals. NTM incidence was not significantly different between Hispanic and non-Hispanic individuals. ADI state rank score was ascertained for 205 of 212 participants. The number of NTM infections observed across ADI scores was highest in the first and third ADI and lowest in the eight ADI; however,

Table 1
Demographic characteristics of Wisconsin children and adolescents with NTM infection, 2011–2018.

	N (%) of persons	Estimated Population < 18 years of age (%)	Cumulative incidence, per 100,000 (95 % CI)
Total	212 (100)	1,316,660	16.1 (13.9–18.3)
Gender			
Female	117 (55.2)	639,423 (48.8)	18.3 (15.1–21.9)
Male	95 (44.8)	669,846 (51.2)	14.2 (11.5–17.3)
Age (years)			
Median (IQR)	3 (1 to 9)		
0 to 2	102 (48.1)		
3 to 5	36 (17.0)		
6 to 8	17 (8.0)		
9 to 11	13 (6.1)		
12 to 14	14 (6.6)		
15 to 17	30 (14.2)		
Ethnicity/ Race			
Hispanic	22 (11.1)	142,175 (10.8)	15.4 (9.7–23.4)
Non-Hispanic	176 (88.9)	1,174,479 (89.2)	15.0 (12.9–17.4)
White	157 (79.7)	1,072,506 (81.5)	14.6 (12.4–17.1)
Black	25 (12.7)	126,741 (9.6)	19.7 (12.8–29.1)
Asian	11 (5.6)	46,249 (3.5)	23.8 (11.9–42.6)
Other	2 (1.0)	–	–
Multiple	2 (1.0)	56,933 (4.3)	3.5 (0.4–12.7)*
Pacific Islander	0 (0)	207 (0.02)	0.0 (0.0–1,780)
Native American	0 (0)	14,019 (1.1)	0.0 (0.0–30)
ADI State Rank Score			
1	31 (15.1)	158,565 (12.2)	23.5 (15.3–31.8)
2	18 (8.8)	157,745 (12.2)	13.7 (7.4–20.0)
3	32 (15.6)	139,470 (10.8)	24.3 (15.9–32.7)
4	17 (8.3)	137,635 (10.6)	12.9 (6.8–19.0)
5	20 (9.8)	120,650 (9.3)	15.2 (8.5–21.8)
6	17 (8.3)	122,165 (9.4)	12.9 (6.8–19.0)
7	24 (11.7)	112,970 (8.7)	18.2 (10.9–25.5)
8	11 (5.4)	110,565 (8.5)	8.4 (3.4–13.3)
9	13 (6.3)	113,550 (8.8)	9.9 (4.5–15.2)
10	22 (10.7)	121,770 (9.4)	16.7 (9.7–23.7)

For individuals with multiple collected samples, characteristics were assessed at time of the first recovered sample. Ethnicity and race data were available for 198 (93.4 %) and 197 (92.9 %) of participants, respectively. ADI scores were available for 205 (96.7 %) of participants. If census block group level was missing, ADI was not assigned. ADI, Area Deprivation Index. 1 = least disadvantaged decile, 10 = most disadvantaged decile. IQR, interquartile range. CI, confidence interval.
*$p < 0.05$ for Fisher Exact test comparing incidence by race with White as reference.

there was no significant difference in cumulative incidence across all ADI groups ($p = 0.068$).

Throughout the study period, there was nonsignificant variation in the annual incidence of NTM infections. The highest annual incidence (3.0 per 100,000) occurred in 2016 and the lowest annual incidence (1.4 per 100,000) in 2013 (Table 2).

Table 2
Annual incidence of NTM infection in Wisconsin children and adolescent, 2011 to 2018.

Year	Annual Incidence (95 % CI), per 100,000 population
2011	1.7 (1.0–2.5)
2012	2.4 (1.5–3.2)
2013	1.4 (0.8–2.1)
2014	1.7 (1.0–2.4)
2015	1.6 (0.9–2.3)
2016	3.0 (2.0–3.9)
2017	2.1 (1.3–2.9)
2018	2.0 (1.2–2.7)

Thirteen NTM species were identified in this study. The most common isolate was MAC (68.8 % of total isolates) (Supplementary Table 1) and the next most frequently identified species were the *M. chelonae-abscessus* group (19.2 % of total isolates). Ninety-five percent of isolates were from skin and soft tissue (57.2 %) or respiratory sites (37.9 %) (Table 3). MAC predominated at most sites and was especially prevalent from skin and soft tissue specimens of the neck (98.3 %). Of interest, several pathogens very uncommon to North America were identified, including 1 isolate of *M. ulcerans*, the agent of Buruli ulcer, and 4 isolates of *M. malmoense*.

4. Discussion

This study of 212 children and adolescents with NTM infection in Wisconsin from 2011 to 2018 is one of the largest contemporary studies of pediatric NTM infection. The characteristics of the children infected with NTM in this cohort are similar to previous reports. Overall, the cumulative incidence of NTM infection among Wisconsin children (16.1 per 100,000 persons) is considerably lower than that reported among the adult population (154 per 100,000 persons) [14]. Predominance of

Table 3
Frequency of NTM species isolated by site of specimen collection.

Site	Total (N = 224) n (%)	Species	n (%)
Respiratory	85 (37.9)	*M. avium* complex	59 (69.4)
		M. chelonae-abscessus grp	13 (15.3)
		M. fortuitum grp	6 (7.1)
		M. mucogenicum	3 (3.5)
		M. franklinii	1 (1.2)
		M. kubicae	1 (1.2)
		M. massiliense	1 (1.2)
		M. nebraskense	1 (1.2)
Skin and soft tissue*—Neck	60 (26.8)	*M. avium* complex	59 (98.3)
		M. malmoense	1 (1.7)
Skin and soft tissue*—Head (non-neck)	42 (18.8)	*M. chelonae-abscessus* grp	19 (45.2)
		M. avium complex	17 (40.5)
		M. malmoense	2 (4.8)
		M. fortuitum grp	1 (2.4)
		M. franklinii	1 (2.4)
		M. marinum	1 (2.4)
		M. massiliense	1 (2.4)
Skin and soft tissue*—Extremity	8 (3.6)	*M. chelonae-abscessus* grp	5 (62.5)
		M. avium complex	1 (12.5)
		M. franklinii	1 (12.5)
		M. ulcerans	1 (12.5)
Skin and soft tissue*—Other	3 (1.3)	*M. avium* complex	2 (66.6)
		M. chelonae-abscessus grp	1 (33.3)
Skin and soft tissue*—Unspecified	15 (6.7)	*M. avium* complex	10 (66.6)
		M. chelonae-abscessus grp	3 (20.0)
		M. chimera-intracellulare	1 (6.7)
		M. malmoense	1 (6.7)
Musculoskeletal	3 (1.3)	*M. chelonae-abscessus* grp	2 (66.6)
		M. kansasii	1 (33.3)
Gastrointestinal	2 (0.9)	*M. avium* complex	1 (50)
		M. mucogenicum	1 (50)
Blood	1 (0.4)	*M. mucogenicum*	1 (100)
Mediastinal	1 (0.4)	*M. avium* complex	1 (100)
Unspecified	4 (1.8)	*M. avium* complex	4 (100)

*‘Skin and soft tissue’ includes specimens labeled as ‘lymph nodes’.

NTM infections in the first few years of life has been well described [23,24], particularly for NTM lymphadenitis [25–34]. That age distribution was again demonstrated in this study. There was also a slight predominance of infections in females. A number of other pediatric NTM studies have reported higher frequency of infections in females [23,25–27,29,30,32,34–36]; conversely, a few studies report essentially equal rates of NTM infection in males and females [24,28,33]. In adults, women have a higher frequency of NTM infection compared to men [8,37], for which some authors have proposed a mechanism linked to sex hormones [38]. By contrast, there is no explanation or even a proposed hypothesis as to why pediatric NTM infections are more prevalent in females. This sex-specific pattern deserves further investigation.

Other risk factors for NTM infection evaluated in this study were race/ethnicity and socio-economic disadvantage (ADI score). Proportionally, Wisconsin's pediatric population is more diverse than the adult population, with markedly greater proportions of Asian, Black, multiracial, and Hispanic individuals in the pediatric population (Supplemental Figure 1). NTM infection rates were significantly lower in multiracial children with only two individuals in this group reported. Though statistically non-significant, Asian and black participants had higher rates than white participants, similar to what we have reported for the adult population in Wisconsin [14]. The lack of NTM infections reported in Native American and multiracial children during the eight-year period may represent lower risk for exposure or NTM disease, inaccurate reporting of race/ethnicity to healthcare providers, or disparities in access to health care. Though non-significant in this study due to low case numbers, the highest cumulative incidence of NTM infection observed in Asian participants is similar to recently reported findings in adults with NTM infection [14,39]. The tendency toward higher incidence among children in *advantaged* ADI scores, and the lack of significance in the variation of NTM incidence across ADI scores, contrast with a recent report on NTM infection in Wisconsin adults, in whom a higher incidence of NTM infection was found in individuals in *disadvantaged* ADI rank scores [14]. Possible causes of higher NTM incidence in advantaged children could be underdetection of NTM infections in disadvantaged groups due to differences in care-seeking behavior or disease diagnosis in such children or lower overall access to healthcare. Further investigation of pediatric NTM infection by race/ethnicity and socioeconomic status in the United States is warranted.

Because NTM infections are inconsistently reported and some NTM infections may be associated with minimal symptoms, the true burden of NTM infections in children is not well understood. A recent review of 11 studies of pediatric extrapulmonary NTM infection reported estimated annual incidence rates of 0.08 to 4.5 per 100,000 [16]. The annual incidence reported in this study, which includes pulmonary cases, is within that range. Two previous epidemiologic reports of pediatric NTM infections reported lower proportions of pulmonary disease (14 % and 23 %) [31,40] compared to the finding of 38 % of isolates being from respiratory specimens in this study. This discrepancy may be explained by reliance on clinical diagnoses of pulmonary NTM disease in those reports, compared to our study's reliance on laboratory isolation of NTM. Some reports largely reliant on data from adults have suggested that the incidence and prevalence of NTM infections is increasing across the United States [4,5,41], Canada [6,7], Europe [3,9,10], and Asia [42,43]. National data from Finland between 1995 and 2016 [35] and from France between 2004 and 2013 [36] demonstrated sharp increases in the annual incidence of childhood NTM infections which coincided with discontinuation of routine Bacilli Calmette-Guérin (BCG) vaccination in each country (in 2006 and 2007, respectively). Reports of NTM adenitis in children cared for in hospitals in Montreal, Canada and Athens, Greece showed significant increases in incidence from the 1990s to 2000s [44] and the 1980s to 1990s [28], respectively. However, more recent population-based studies of pediatric NTM infection in Queensland, Australia [23] and Sweden [25] during an era in which BCG vaccination was not routine, do not show increasing annual incidence. In the present study, we observed only minor variation, which was not statistically significant, in annual incidence of pediatric NTM infection between 2011 and 2018.

For both skin and soft tissue (including lymph node specimens) and respiratory infections, MAC was the most common NTM isolated in this study. In recent studies of NTM lung disease and lymphadenitis, MAC has been reported to be the most common species infecting children and adolescents [16,29,30,35,36,45]. However, older studies have described rapid growers, such as *M. abscessus, M. chelonae,* and *M. fortuitum,* as the most frequent cause of pediatric skin and soft tissue infections and rarely reported MAC. In our study, rapidly growing NTM, namely *M. chelonae-abscessus* group, were the most frequently reported NTM from skin and soft tissue infections of the head (non-neck) and extremities. Cervical lymphadenitis is typically described as the most common presentation of NTM infection in children [16,24,31,34]. In the database used for this study, specimen site was inconsistently provided on the laboratory reports (these samples were sometimes more generally reported as "skin and soft tissue," rather than "lymph node," for example). Therefore, we describe skin and soft tissue infections more broadly, inclusive of lymphadenitis. However, it should be noted that skin and soft tissue specimens derived from the neck largely represent cases of cervical lymphadenitis in this study, and are dominated by MAC as seen in other recent reports [31,40].

The recovery of *M. ulcerans* from a single skin and soft tissue specimen and four instances of *M. malmoense* isolation from skin and soft tissue sites are notable, as these pathogens are rarely reported in North America. *M. ulcerans* is a tropical pathogen that causes Buruli ulcer, a chronic, disfiguring skin condition, sometimes involving contiguous muscles, tendons, and joints. Fewer than 10 cases per year occur in the Americas [46]. The vast majority of Buruli ulcer cases occur in rural areas in central or west Africa, Australia, Asia and the Pacific [46,47]. The infection documented here was most likely imported from outside the United States. *M. malmoense* is a prevalent NTM pathogen in Europe and is usually associated with pulmonary NTM disease, but it is extremely uncommon in North America [48–51]. The report here of multiple *M. malmoense* skin, soft tissue, and lymph node infections in Wisconsin children adds to a small body of literature describing *M. malmoense* as an important minority NTM in North America.

A strength of this study is the use of WEDSS, a comprehensive, state electronic database. Wisconsin mandates reporting of mycobacterial infection, which is accomplished primarily through laboratory reporting into the WEDSS database. Our data therefore represent a reasonable estimate of total pediatric NTM infections in Wisconsin. Our study has important limitations. First, as a laboratory reporting-based study, clinical data, including symptoms, medical history, and imaging findings, were lacking. The absence of these data may present challenges in ascribing clinical relevance of the findings presented. Second, as described above, specimen type and site were not consistently provided in the laboratory reports, and therefore lymph node specimens were included in the more general category of skin and soft tissue infections. Third, as described in the Methods, techniques for laboratory identification of NTM at the species and subspecies level evolved over the study period. Most notably, distinctions between (1) *M. chimaera* and *M. intracellulare* and (2) *M. abscessus* and *M. chelonae* were technically infeasible during most of the study period. Future epidemiologic studies will likely be able to discriminate individual species of particular clinical relevance using molecular identification [52]. Finally, this study was not large enough to allow analysis of potential association of NTM infection within ADI groups stratified by race/ethnicity or vice-versa.

In summary, this comprehensive analysis of the NTM isolates from children and adolescents in Wisconsin advances our understanding of pediatric NTM epidemiology in several ways. Consistent with previous findings, we show that children are particularly vulnerable to NTM skin and soft tissue (including lymphadenitis) infection in the first few years of life. Our data provide additional evidence that NTM infection is more frequent in female children. We call for further research to identify the underlying cause of this apparently elevated risk. Similar to other recent

pediatric studies, we found no significant increase in annual incidence over the study period. Though we did not find conclusive associations between race/ethnicity or socio-economic status and NTM infection, these factors should be further explored in larger pediatric studies of diverse U.S. populations.

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Author contributions

DG, SGB, and EAM conceived of the study. BJV, DG, SGB, and EAM designed the study. JTK and SGB acquired the data. BJV, DG, BCA, and SGB analyzed the data. BJV, DG, and EAM interpreted the data and drafted the manuscript. All authors provided intellectual input in the the manuscript revisions.

Ethical statement

The study design and use of de-identified human data were approved by the Wisconsin Department of Health Services and the Institutional Review Board of the University of Wisconsin School of Medicine and Public Health.

CRediT authorship contribution statement

Bryan J. Vonasek: Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Danièle Gusland:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Julie Tans-Kersten:** Conceptualization, Data curation, Resources, Writing – review & editing. **Elizabeth A. Misch:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Suzanne N. Gibbons-Burgener:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100456.

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