Non-tuberculous mycobacterial skin and soft tissue infections in the Northern Territory, Australia, 1989-2021.

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Highlights

- There is an increasing incidence of NTM skin/soft tissue disease.
- *M. fortuitum* most common NTM causing cutaneous disease in Northern Territory (NT).
- In the NT most cutaneous NTM cases have been acquired in urban areas.
- Typical cutaneous NTM cases may have no risk factors other than trauma.
- Aboriginal individuals are underrepresented compared to population estimates.

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Key words:
Nontuberculous mycobacteria, Northern Territory, skin, soft tissue, cutaneous

Abstract

Background

A previous review demonstrated that the majority of NTM infections in the Northern Territory (NT) are pulmonary in nature,[1] however skin and soft tissue (SST) are likely the next most common sites of disease. The current epidemiology of NTM SST infections across the NT is not known. We aimed to establish the current and historical incidence rates, and the organisms involved.

Methods

All NTM cases reported to the Centre for Disease Control in Darwin from 1989-2021 were retrospectively reviewed.

Results

226 NTM notifications were reviewed. 73 (32%) cases were SST infections. The incidence of SST cases increased over the study period. Female cases were more common (p=0·002). Disease occurred across a wide age range (1-85 years). Only 16% of cases occurred in Aboriginal individuals. Many cases had no clear provocation, but localised trauma was the most common risk factor. The most common organism identified was *M. fortuitum (*41%). Diagnosis was often delayed, with a median time to diagnosis of 69 days (IQR=31-149). Most cases (60%) underwent surgical intervention with adjunctive anti-mycobacterial medical therapy.

Conclusion

NTM SST incidence rates increased over the study period. NTM SST infections are a rare but important differential diagnosis for non-healing cutaneous wounds.

Non-tuberculous mycobacterial skin and soft tissue infections in the Northern Territory, Australia, 1989 – 2021

Background

Non-tuberculous mycobacteria (NTM) are acid-fast bacilli widely present in natural environments such as soil and water.[2-5] NTMs are also known as ‘environmental mycobacteria’, or ‘atypical mycobacteria’, and are classified as mycobacteria that do not cause tuberculosis (TB) or leprosy. NTMs are often divided into rapid growing (those that can form mature colonies on agar plates in less than 7 days) or slow growing

species.[4, 6] Clinical manifestations of disease varies depending on the species involved, and how rapidly each reproduces. NTMs can cause an array of clinical disease, including pulmonary infections, lymphadenitis, skin and soft tissue (SST) infections, osteomyelitis and disseminated disease.[4]

The NTM species widely known to cause SST infection include: *M. ulcerans, M. avium complex, M. abscessus, M. kansasii, M. chelonae, M. fortuitum,* and *M. marinum*.[7, 8] NTM SST infections occur when organisms enter through a break in the skin, usually from trauma or as a complication of a surgical procedure.[8] Cutaneous and soft-tissue involvement can also occur as a consequence of a disseminated mycobacterial disease, particularly in immunosuppressed patients.[7]

Diagnosis of an NTM SST infection requires the presence of acid-fast bacilli on microscopy, culture and/or polymerase chain reaction (PCR) testing from a skin swab or tissue biopsy.[2, 9] Early identification is important, as many empirical antibiotic regimens will not adequately treat NTM disease.[7] Treatment for any NTM infection often requires multiple antimicrobial agents.[10] These agents are often associated with clinically significant adverse side effects and are generally administered for prolonged periods.[10] Despite the risk, these agents are used and side effects managed with the aim to prevent progression of infection to deeper structures such as tendon, ligaments and bone.[11] Management often involves surgical resection of NTM SST disease, either alone or as an adjunct to antimicrobial agents.[11] In some circumstances antibiotics alone may be used.[11] There is limited existing data to guide the management of NTM SST infections and treatment is highly individualised.

Despite the complexities in diagnosis, global estimates have demonstrated increasing rates of NTM infections.[12, 13] This has been attributed to the changing climate, specifically, warmer weather and increasing rainfall.[13] NTM disease is more common in the tropics;[14] however some organisms have been found in more temperate environments.[2] The Northern Territory (NT) is a sparsely populated region in northern Australia, with the population increasing from 161,179 people in 1989 to 249,200 in 2021. The NT has two contrasting climates; the northernmost 'Top End' region is tropical, with a monsoonal, hot summer 'The Wet' and an arid, warm winter 'The Dry'. The 'Central' region is a semi-arid desert with cooler winters. It has been predicted that rates of SST may increase in the NT,[1] but it is unclear how the changing climate has influenced the rates of NTM disease to date.

The NT has a large Aboriginal Australian population, among whom morbidity and mortality from many infectious diseases are higher than among the non-Aboriginal population.[15] Previous research has demonstrated Aboriginal Australians will likely be disproportionately affected by climate-sensitive infectious diseases in the future,[16] which may include increased rates of NTM disease.

In Australia, an infection with any NTM species is a notifiable disease in the NT, Queensland, and South Australia. A previous review explored all notified NTM cases from the NT between 1989-1997, and demonstrated the majority of infections were pulmonary in nature.[1] Fifty-eight cases of NTM disease were reported in this period, with an average yearly incidence of 3·9 cases per 100,000 persons. Of these cases only 9 were cases of SST disease.[1] The current scope of reported NTM SST infections in the NT is not known. This paper aims to describe the epidemiology of NTM SST infections in the NT between 1989 and 2021, specifically the incidence rates in various categories, the NTM species involved, and treatment outcomes.

Methods

All NTM cases reported to the Northern Territory Centre for Disease Control (CDC) between 01/01/1989 – 31/12/2021 were included in the retrospective study. Data was obtained from the NT Notifiable Diseases System (see Figure 1). Electronic medical records and hard copy notification forms were also obtained to cross-reference notifiable disease data. Cases where microbiological samples were obtained from sites other than skin were excluded. Cases of NTM SST infection were included if they met all three of the following criteria:

1. Detection of non-tuberculous mycobacterium by culture or nucleic acid testing from a non-healing skin lesion;
2. Clinical presence of a non-healing skin lesion or soft tissue infection; and
3. Other disease processes had been reasonably excluded (e.g. tuberculosis, malignancy).

Cases were reviewed to determine the NTM species involved. Species were categorised as either rapid growers (*M. abscessus, M. chelonae, M. fortuitum, M. smegmatis, M. mucogenicum*) or slow growers (all other species).[11] In cases where both fast and slow species were isolated, they were categorised by the primary organism identified. Cases were deemed to be immunosuppressed if they were a recipient of a solid organ or haematological stem cell transplant, or if they had a history of immunosuppressive medication use, human immunodeficiency virus (HIV) co-infection, active cancer or end-stage renal disease. As per the NT guidelines, immunosuppression included use of greater than 15 milligrams of prednisolone (or corticosteroid equivalent) per day for more than 2 weeks.[9]

Cases notified in other jurisdictions were not included in analysis. Cases acquired by NT residents travelling outside of the NT (but not notified elsewhere) were included as imported cases. Cases were considered to be urban if the disease was acquired in the greater Darwin region or Alice

Springs, with all other regions in the NT considered rural. Cases were classified by season of onset either as 'The Wet' (September – April) or 'The Dry' (May – August). Clinical management of cases and treatment outcomes (rates of cure, recurrence despite treatment, loss to follow-up, and death) were reviewed.

To determine rates, data from the Australian Bureau of Statistics (ABS) residential population was used.[17] For 11 year comparison, the denominator used for these calculations was the NT population recorded for 1999, 2010, and 2021 respectively. We report number and proportion, and statistical tests report odds ratio as the measure of association (P<0·05 considered significant). Descriptive and statistical analyses were performed in STATA version 17.

Results

Between 1989 and 2021, a total of 226 NTM cases were notified which included 73 (32%) cases with SST involvement. The incidence of SST cases increased from 6·1 cases per 100,000 people (1989-1999) to 10.0 cases per 100,000 people (2000-2010), and subsequently to 15·2 cases per 100,000 (2011-2021) (Figure 2). There was a 1·7-fold increase (95%CI=1·1-2·5) in incidence rates from 1989-1999 to 2000-2010, and a 2·2-fold increase (95%CI=1·9-4·1) between 1989-1999 and 2011-2021 (Figure 2b, Supplementary Table 1). The highest yearly incidence was in 2004 (4·4 cases per 100,000 people), when a geographical cluster of five *M. fortuitum* cases was detected in urban Darwin. In 2021, the incidence was 2·0 NTM SST infections per 100,000 people in the NT.

Demographics and clinical characteristics are shown in Table 1. SST disease occurred across a wide age range (range = 1-85 years). There was a significant gender difference, with more female cases (n=43, 59%) than male (n=30, 41%) ($p \leq 0{\cdot}002$). Most NT cases (n=62, 85%) were from the Top End, with 8 cases (11%) from Central Australia. Only 3 cases (4%) were acquired outside of the NT. The majority of cases (n=51, 70%) were acquired in urban locations. No seasonal variation was observed in the onset of cases, even when analysing only cases observed in the tropical Top End climate. Only 12 (16%) cases occurred in Aboriginal Australians ($p \leq 0{\cdot}001$). The majority of clinical infections occurred on the distal limbs, with a small proportion occurring on the abdomen (11%), chest (8%), and face or neck (7%).

From the 73 SST cases, 13 different species of NTMs were isolated. This included 5 cases in which multiple organisms were detected (Supplementary table 2). The most common causative organisms were *M. fortuitum* (41%), *M. abscessus* (15%), and *M. ulcerans* (10%). There were 49 instances where a rapid growing species was isolated, compared to 30 instances involving a slow growing species.

Of the 73 SST cases, 36 (53%) had no clear provocation or documented risk factors. As seen in Table 2, the most common risk factor preceding NTM SST infection was skin trauma (n=28, 38%). Of these 28 cases with skin trauma, a laceration or penetrating wound was the most commonly reported injury (n=9/28, 32%) followed by a surgical procedure (n=8/28, 29%). Animal and insect bites were less frequently reported (n=2, 7% and n=3, 11% respectively). Non-trauma related risk factors were not consistently documented, but 37% of cases (n=27) had at least one associated medical risk factor and some of these also had skin trauma. Risk factors included: a history of diabetes (n=11); immunosuppression other than HIV (n=9); current smoker (n=7), and HIV infection (n=5).

The median time to diagnosis for all cases was 69 days (IQR=31-149) with rapid growing species identified earlier than non-rapid species (mean=90 vs 175 days respectively, p=0·05). There was no significant difference in time to diagnosis by Aboriginal status or remoteness. There were 27 patients (38%) hospitalised for inpatient management. Although not statistically significant, cases were 2·8 times more likely to be admitted to hospital if they had a medical risk factor (p=0·07, 95%CI=0·89-8·6). The median time spent in hospital was 4 days (IQR=2-19) and the mean treatment time with anti-mycobacterial agents for all cases was 17·9 weeks (range=0·5-52). While mean antibiotic duration for slow growing species was 13 weeks (95% CI=9·9-16·1), and 20 weeks (95%CI=14·3-26·5) for rapid growing species, the difference was not significant (p=0·06).

Clinical management and treatment outcomes are summarised in Table 3. Overall, 54/73 (74%) of cases underwent surgical intervention. A small number of cases had surgical resection alone (n=9, 14%), however the majority of individuals received a combination of anti-mycobacterial agents and surgical management (n=44, 60%). There was no statistical difference in undergoing surgical management when comparing rapid or slow growing species.

There was no significant difference in poorer short-term outcomes (defined as disease recurrence, or surgical re-excision) where time to diagnosis was equal to or greater than the median time to diagnosis (p value=0·8). Longer term outcomes (such as late disease recurrence) were difficult to establish due to insufficient documentation.

Cases where surgical management was the only intervention were associated with good outcomes (n=9, 90% cure rate). A large number of records (n=32, 43%) did not have any outcomes documented. Where outcome data was available, 34/41 cases (83%) were deemed to be cured after initial management. Four cases (5%) demonstrated evidence of disease recurrence. At the time of review, one case was still undergoing active treatment.

There were three deaths due to NTM infection (4%). All three individuals who died were immunosuppressed and were greater than 70 years of age. Two of the three deaths were associated with disseminated NTM infection (with disseminated defined as NTM cultured from blood or from skin/soft tissue plus another site). Overall, there were 4 cases of disseminated mycobacterial infection with skin involvement recorded, and 3 (75%) had documented medical risk factors.

Discussion

In line with previous findings and projections,[1] the incidence of NTM SST disease in the NT has increased over the last thirty-three years. When comparing the incidence rates of three eleven-year periods, our rate ratio of 2·2 is similar to studies from the United States, which have shown a threefold increase in the incidence of cutaneous NTM infections.[18] Similarly, studies from Thailand[3] and other reports from around the globe indicate rising NTM SST infection rates.[8]

It is possible that increased rates may reflect improved disease recognition and increased availability of testing modalities such as PCR. Other studies have asserted the changing climate has likely contributed to an increase in case numbers.[13] It is well recognised that many NTM

related infections commonly occur in warm tropical climates.[1] Seasonal variation has also been shown to be associated with infections caused by certain mycobacterial species. *M. ulcerans* disease has been observed in temperate regions of southern Australia, with most infections diagnosed in summer and autumn.[19] The precise mechanisms are unclear, but clothing and skin exposure may be factors contributing to seasonality. Although our data does not demonstrate a clear seasonal variance, the majority of our NTM cases were found in the warmer, tropical Top End region. Relatively fewer cases were observed in the southern semi-arid desert region that experiences colder winters and this raises concern of possible disease spread in the context of future global warming due to climate change.

Further epidemiological data is needed to inform and predict the impact of the environment on NTM infections. Notifiable disease data can be used to identify evolving outbreaks and local clusters. To date, only one cluster of cutaneous NTM infections has been identified in the NT, and this was in the tropical Top End. As demonstrated by the peak in Figure 2a, a cluster of five *M. fortuitum* cases was observed in 2004. These cases all occurred in young children, with cases residing in Palmerston (a satellite city expanding with considerable construction just outside of Darwin). Public health investigation found that all cases were associated with water exposure, with some reporting prior insect bites. Cases were most likely related to residential building developments that disrupted the local environment, but no definitive cause was established.

Previous studies have demonstrated the isolation of NTM species from water supplies and soil.[20] In future, environmental prevalence data on the presence of NTMs may be a useful tool to supplement human disease data. We found that *M. fortuitum* was the most common NTM organism to cause SST infections in our cohort. *M. fortuitum* is frequently associated with skin, soft tissue and bone infections, and is found in natural and processed water, sewage, and dirt.[11]

The frequency and distribution of NTM species causing SST disease varies across geographical locations. *M. fortuitum* was the most common organism identified in the NT, while other studies in Thailand have reported *M. abscessus* (the second most common in the NT) as the primary species associated with SST infections.[3] In the United States, one review of SST infections found *M. marinum* the commonest organism identified.[18] *M. marinum* was relatively uncommon in our study. Our third most common organism was *M. ulcerans.* Previous studies have shown *M. ulcerans* typically occurs in discrete geographical locations in Queensland and Victoria;[19] however this review of more recent data demonstrates at least 7 cases where acquisition was in the NT.

Aboriginal people had significantly lower rates of NTM SST compared to the wider population. While it is important to consider the low rates of NTM SST disease in Aboriginal Australians could represent under ascertainment or underreporting, other environmental and immunological factors are likely contributing to fewer case numbers. Our findings concord with a previous review which found that Aboriginal Australians had lower rates of NTM lymphadenitis and pulmonary disease.[1] It has been suggested that immunity to mycobacteria species might have a common basis and thus prior *M. tuberculosis* infection may confer some protection against NTM disease.[1] Although the Aboriginal community in the NT face a higher burden of *M. tuberculosis* infection than the non-Aboriginal population,[21] on global terms *M. tuberculosis* infection rates are quite low in Australia.[21] BCG (Bacille Calmette–Guérin) vaccine has been recommended for Aboriginal and Torres Strait Islander children aged <5 years in some parts of Australia, and was routine policy in the NT until the end of 2015. This may have influenced the rates of disease we have observed. A previous meta-analysis demonstrated that BCG offers protection for NTM lymphadenitis, although the effects on cutaneous disease are less clear.[22] Lower reported rates of NTM disease in Aboriginal peoples contrasts other communicable

diseases, such as group A streptococcus, where social factors such as overcrowded housing and poorer socioeconomic status have influenced higher levels of disease transmission. This supports previous assertions that NTM are not transmitted person-to-person.

Theories regarding the transmission of NTM disease are complicated and often controversial. There have been suggestions that animal vectors may explain the spread of *M. ulcerans* in southern Australia.[23] Transmission of mycobacteria via insect bites has also been explored.[24] One in-vitro study found that very low doses of *M. ulcerans* can penetrate through a mosquito bite wound and may be sufficient to cause clinical disease.[24] Our data documented three cases where insect bites were associated with an NTM SST infection. Compromised skin integrity from a bite and/or a subsequent scratch is likely more important than direct transmission from a vector, however further investigation is needed.

Our data are in line with the existing literature which demonstrates that the most common risk factor for developing NTM disease is skin trauma or a penetrating injury.[18] The body site distribution of disease (which was predominantly the distal limbs), together with trauma being the most commonly reported risk factor, indicates that NTM SST disease appears to be the result of opportunistic infection following skin breach.

Skin breach can also occur in the context of a surgical procedure, and mycobacterial infection following medical intervention is not uncommon.[11] Given 29% of our cases with preceding skin trauma were associated with a recent surgical procedure, iatrogenic transmission is an important consideration for clinicians. Previous case reports describe NTM SST infections following cosmetic procedures, where contaminated water was used to clean medical instruments.[5, 6] Although not seen in our cohort, increasing rates of cutaneous NTM infections have been attributed to the increasing popularity of cosmetic injections and tattoos in some countries.[25]

Previous studies have demonstrated an association between NTM disease and immunosuppression and/or HIV infection.[1] Most existing research investigating potential NTM risk factors relates to pulmonary disease. While medical risk factors were incompletely recorded for many of the historical cases in our dataset, immunosuppression and/or diabetes were the most common risk factors. Establishing the significance of these factors on disease outcomes was limited by small numbers.

Mortality from NTM SST is uncommon, and all deaths associated with NTM SST disease occurred in elderly individuals who were immunosuppressed. One of the deaths occurred in a patient with an infected peritoneal catheter site, whilst the two others had skin involvement associated with disseminated NTM infection. One of the individuals with disseminated infection had been receiving medically indicated high dose glucocorticoids and developed pustular lesions on the face and arms. The patient died with sepsis from an unknown source, however several blood cultures, a sputum sample, and a skin biopsy demonstrated growth of *Mycobacterium chelonae* posthumously. *M chelonae* is a rapidly growing NTM and has been described to cause disseminated infection in immunosuppressed individuals.[11] Although a rare diagnosis, disseminated NTM infection can present with skin lesions,[26] and can be fatal in the setting of innate or induced immunosuppression.[27]

Diagnosis of an NTM infection was delayed in many of the cases. The median time to diagnosis of 69 days mirrors findings from other studies, and suggests that NTM SST is often only considered once all other alternative diagnoses have been exhausted. Delays in diagnoses more commonly occur when patients present outside of known NTM endemic areas, suggesting a lack of awareness amongst patients and clinicians.[28] There is limited evidence assessing how delays affect outcomes, however delayed diagnosis of *M. ulcerans* has been associated with increased morbidity.[29]

Once an SST infection is diagnosed, clinical management is guided by the implicated NTM species. Certain NTM organisms such as *M. marinum (*and in most cases *M. ulcerans)* may be cured with antimicrobials alone,[11, 29] whereas others species such as *M. fortuitum* usually require surgical intervention.[11] There is limited data to inform clinical guidelines, but most typically rely on surgical management and adjunctive anti-mycobacterial agents directed by susceptibility testing.[9] Where surgical resection alone was undertaken in our series, 90% of cases had clear documentation of cure. Good outcomes have been described for a combination of medical therapy and surgery,[1] and our observed cure rates support this but are limited by small numbers. Treatment regimens are often highly individualised, and larger cohorts with well-defined usage of anti-mycobacterial agents and species-specific data is needed.

Although large datasets on *M. ulcerans* exist, our data represents one of the largest reviews to date of skin and soft tissue infections caused by a variety of NTM species. This study is limited by the inherent difficulties in retrospective case reviews and the potential for under ascertainment of cases. Despite this, our epidemiological profiles add to the existing literature. We describe a wide age range of cases, and our cases were more commonly females with no risk factors other than skin trauma. There was a rising incidence of NTM SST disease in the NT. A cluster of NTM SST disease occurred in 2004 with suggestive causative factors identified but no definite links established, in contrast to outbreaks elsewhere. Ongoing awareness and support for public health notification of all NTM cases will be crucial in the early detection of potential NTM SST outbreaks. Ultimately, it is important for clinicians to consider NTM SST infections as a rare but important differential diagnosis with the need for early testing of non-healing cutaneous wounds.

Statements

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Table 1. Demographic and clinical characteristics of NTM SST infections, 1989-2021.

Demographics%		
Total	**73**	**100**
Age group (years)		
0-9	10	14%
10-19	5	7%
20-29	6	8%
30-39	16	22%
40-49	13	18%
50-59	12	16%
60-69	7	10%
70-79	2	3%

80-89	2	3%
Sex		
Female	43	59%
Male	30	41%
Aboriginal status		
Non-Aboriginal	60	82%
Aboriginal	12	16%
Unknown	1	1%
Body site affected		
Lower limb/foot	31	43%
Upper limb/hand	21	29%
Abdomen	8	11%
Chest	6	8%
Face/neck	5	7%
Unknown	2	3%
Remoteness of NT cases		
Urban	51	70%
Rural	19	26%
Imported	3	4%
Season of onset		
Wet	28	38%
Dry	26	36%
Unknown	19	16%

Table 2. Medical and trauma related risk factors amongst NTM SST cases

Medical risk factors[a]	**n/N**	**%**
Diabetes	11/73	15%
Immunosuppressed (other than HIV)	9/73	18%
Current smoker	7/73	10%
HIV infection	5/73	7%
Types of preceding skin trauma	n/N	%
Penetrating wound	9/28	32%
Surgical procedure	8/28	29%
Insect bite	3/28	11%
Animal bite	2/28	7%
Other skin trauma	6/28	21%

[a]*Some individuals had more than 1 medical risk factor*

Table 3. Treatment outcomes by NTM species and management options

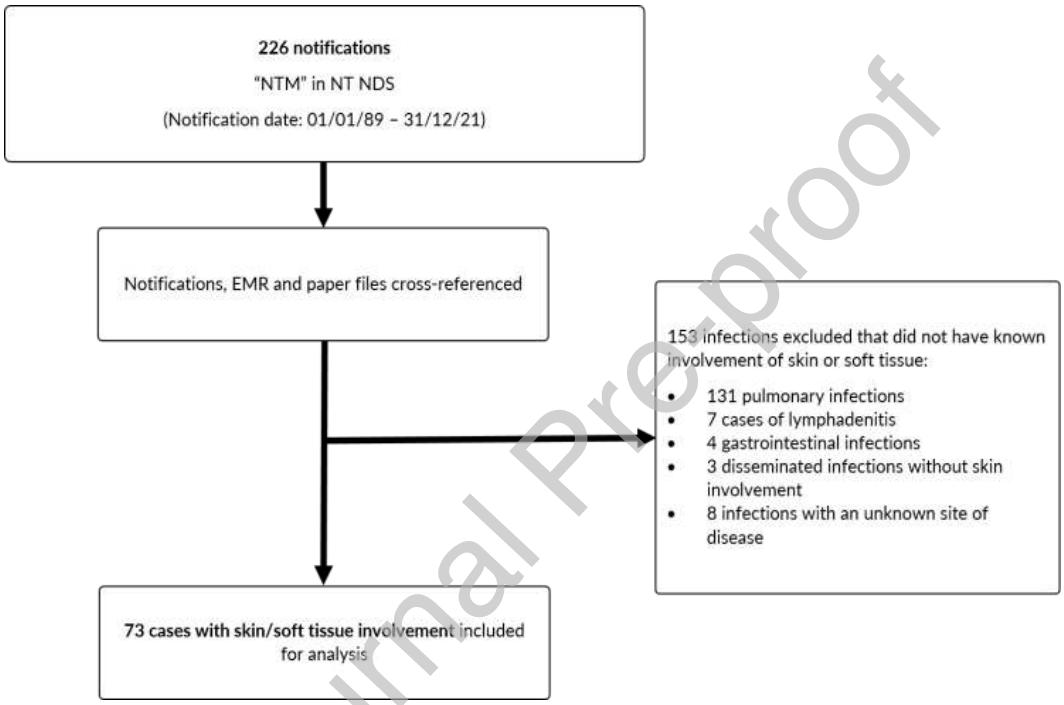
	Cured	**Recurrence**	**Died**	**Missing/ Lost to follow up/Ongoing**[a]	**Total (n=73)**

NTM species type (rapid or slow growers)						
	Rapid growers	**24**/73 (33%)	**3**/73 (4%)	**2**/73 (3%)	**18**/73 (25%)	**47**/73 (64%)
	Slow growers	**10**/73 (14%)	**1**/73 (1%)	**1**/73 (1%)	**14**/73 (19%)	**26**/73 (35%)
	Combined	**34**/73 (47%)	**4**/73 (5%)	**3**/73 (4%)	**32**/73 (44%)	**73**
Clinical management						
	Surgery alone (resection)	**9**/10 (90%)	-	-	**1**/10 (10%)	10/73 (14%)
	Antibiotics & Surgery[b]	**22**/44 (50%)	**4**/44 (9%)	**1**/44 (2%)	**17**/44 (38%)	**44**/73 (60%)
	Antibiotics alone	**3**/12 (25%)	-	**2**/12 (17%)	**7**/12 (58%)	**12**/73 (16%)
	Not documented	-	-	-	**7**/7 (100%)	**7**/73 (10%)

[a] *1 rapid NTM case had ongoing treatment in the study period*

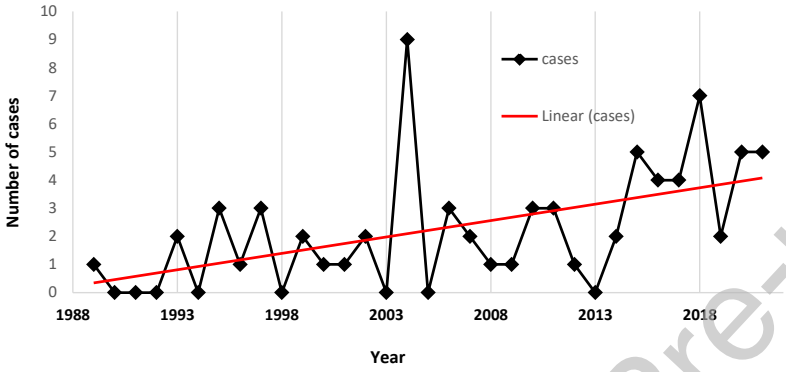
[b] *includes resection and or debridement*

Figure 1. NTM notifications analysed

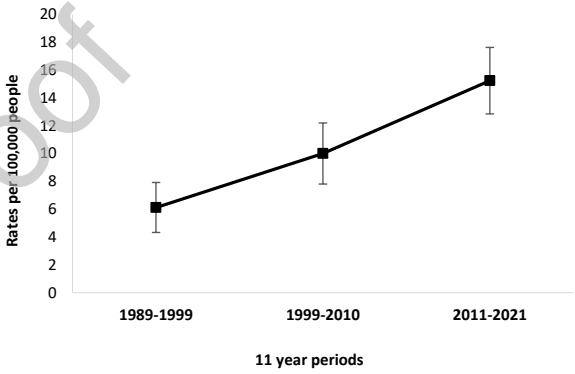


NTM = non-tuberculous mycobacterium
NT NDS = Northern Territory Notifiable Diseases System

Figure 2.



a. Epicurve of infections notified in the Northern Territory, 1989-2021.



b. 11-year incidence rates of infections, with 95% confidence intervals

NTM = non-tuberculous mycobacterium
SST = skin and soft tissue

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: