HEALTH CARE UTILIZATION AND COSTS IN A SAMPLE OF REFRACTORY PULMONARY NONTUBERCULOUS MYCOBACTERIAL PATIENTS WITH POSITIVE AND NEGATIVE SPUTUM CULTURE IN CANADA, FRANCE, GERMANY, AND UNITED KINGDOM

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Background

Nontuberculous mycobacterial pulmonary disease (NTMPD) is a rare but emerging global health concern, with important public health implications.[1,2] The infection is caused by ubiquitous mycobacteria found in the soil and water.[3] Over 150 species of NTM have been identified and Mycobacterium avium complex (MAC) has been reported to be the most common causative agent in NTMPD worldwide.[3]

Treatment of NTMPD consists of a long-term course of multi-drug antibiotic regimen; however, patients who are not responsive to first-line therapy have limited therapy options.[1] Currently, data quantifying the cost of NTMPD over the course of the illness are sparse,[4,5] and for patients who are refractory to treatment, the economic burden is unknown. Moreover, it has not yet been investigated how sputum culture testing status is associated with healthcare resource use and associated costs.

We aimed to estimate NTMPD-related resource use and direct medical cost at three stages of NTMPD: while having positive sputum culture, during negative sputum culture, and while considered cured.

Methods

Study Design:

We conducted a retrospective observational survey of physicians in **Canada, France, Germany**, and the **United Kingdom** (UK), to collect practice patterns and health care resource utilization data among patients with refractory NTMPD caused by MAC over a 24-month period.

While protecting patient identity, qualified physicians referred to eligible patients' charts to collect information about patients' treatment history for NTMPD-related health care resource utilization. Physicians were asked in an online survey to extract the relevant information from those charts for up to 5 eligible patients, living or since deceased, who met *all* of the following criteria:

- Must be **infected with MAC**: *M. avium, M. intracellulare,* and/or *M. chimaera*.
- Must be "**refractory**" (i.e., received an antimycobacterial treatment with a reasonable level of treatment compliance AND demonstrated one or more positive cultures after at least 6 months of therapy.)
- Must have received some or all **treatment** any time after September 2013.
- Must **not** have had **cystic fibrosis or have tuberculosis** in the past 24-months
- Must be **primarily under the responding physician's care** for management of NTMPD and not referred to another physician for management.

Data relating to medication use, and diagnostic and post-diagnostic testing for NTMPD were captured from the time of diagnosis to the time of survey completion. Other resource utilization data, including hospital use, physician visits, ancillary care, and other testing, were captured for the 24-month period prior to survey completion.

Categorizing NTMPD disease status

We summarized resource use during three distinct phases of NTMPD:

1) while having positive sputum cultures,

2) from time of first negative sputum culture (along with clinical improvement) to time when considered cured (persistently negative sputum culture for 12 months after onset of negative state); and

3) while considered cured.

The resource utilization collection period spanned 24-months. Trajectories of four hypothetical patients are presented in **Figure 1**, illustrating how sputum culture could have changed during the period of resource utilization collection.

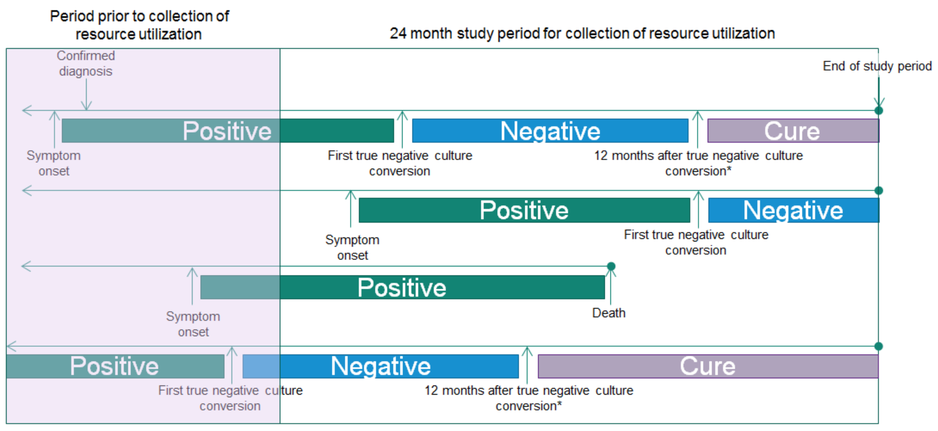


Figure 1. Hypothetical patients' testing status during 24-month resource use collection period

Costing:

We summarized all NTMPD-related resource use and applied unit costs to estimate the total economic burden, from a government health care provider perspective.

Country-specific unit costs in 2015 local currency were obtained from publicly available sources, literature review, and clinical expert consultation. Cost estimates were provided in local currencies; in a pooled analysis across countries, we applied UK unit costs.

Results

In total, 63 physicians provided data (18 from Canada; 16 from France; 13 from Germany; 16 from UK), on a total of 182 patient cases. Overall, the mean (SD) age was 60 years (14), 75% were male, 63% were infected with *M. avium*, 38% had concomitant bronchiectasis and 15% had concomitant HIV/AIDS. Distributions were similar along the NTMPD trajectory.

Average follow-up per patient was 1.5 years; number of patients and time spent at each stage of NTMPD culture status is presented in **Figure 2**.

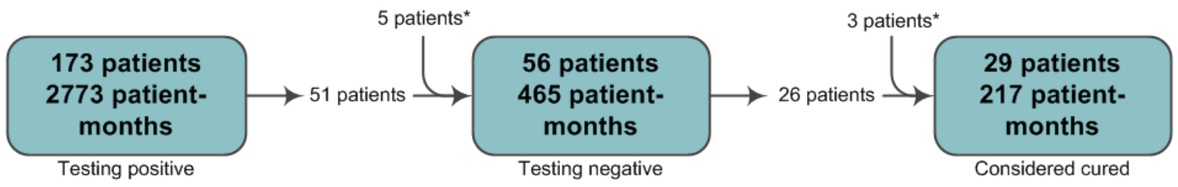


Figure 2. Flow of patients

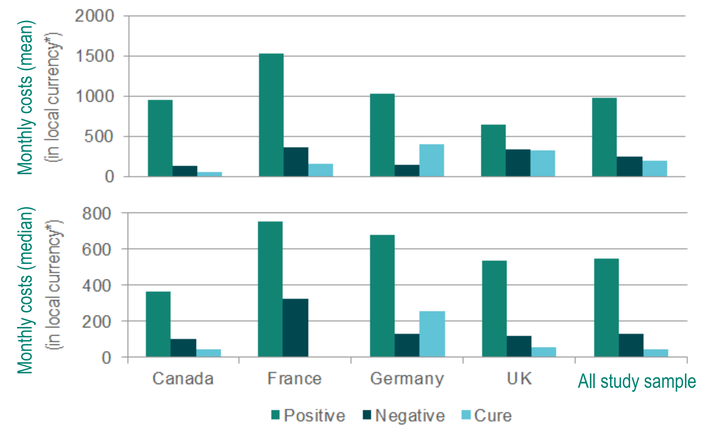
**Patients had negative sputum culture and clinical improvement (N=5) or were considered cured (N=3) prior to beginning the 24-month resource utilization period.*

Results

Costs over the course of NTMPD

Patients with positive sputum culture had the highest costs per month associated with their disease management in all countries. Mean costs were similar for patients with negative sputum culture and considered cured, but this is largely due to right tailed costs (i.e., small number of patients with very high costs), with some patients having costs in a relatively short time they were considered cured.

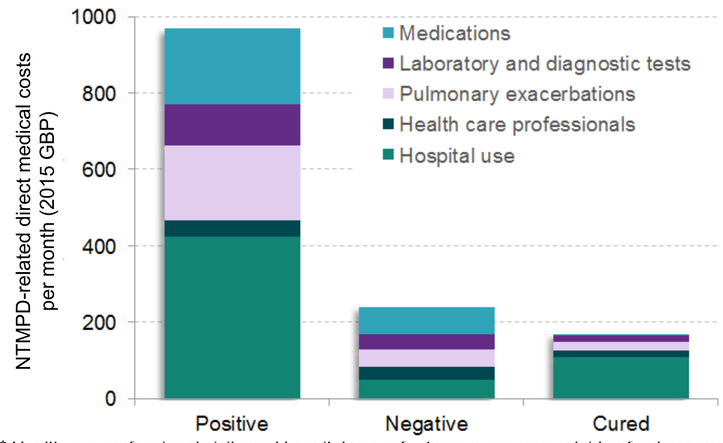
With UK costs applied to all patients, average monthly costs were £970 (standard deviation (SD): £1648) for patients with positive sputum culture, £243 (SD: £296) for patients with negative sputum culture, and £199 (SD: £462) for patients considered cured (**Figure 3**). Median monthly costs were £549, £132, and £47 respectively.



*Canada in 2015 CAD, France & Germany in 2015 EUR, UK and All study sample in 2015 GBP. RU = resource use

Figure 3. Mean and median monthly costs of resource use for patients with positive or negative sputum culture, or cured.

Hospital use contributed substantially to costs during the entire NTMPD cycle, while treatment costs were substantial for patients who had positive or negative sputum culture (but were not yet considered cured) **(Figure 4)**. Pulmonary exacerbations were also major drivers of costs.



** Healthcare professional visits and hospital use refer to resource use outside of pulmonary exacerbations.*

Figure 4. Cost drivers during three NTMPD phases (pooled analysis)

There were some differences among countries in terms of cost drivers:

Canada was the only country among the four with no hospital use or ER visits when patients had negative sputum culture or were considered cured. This contributed to direct medical costs in Canada being 71% lower for patients with negative sputum culture compared to patients with positive sputum culture, and a further 74% lower when patients were considered cured compared to when testing negative.

For other countries, hospital use, medication, and visits to health care professionals were the largest component costs among patients with negative sputum culture or considered cured.

Discussion

Major strengths of this study are that it captured detailed data on NTMPD-related resource utilization for new and existing patients with refractory NTMPD caused by MAC. The data for this study came directly from the charts of physicians who regularly manage NTMPD.

An important **limitation of the study** is that the comparison between the stages with positive sputum culture, negative sputum culture, and cured had a cross-sectional element to it: e.g., of all 182 patients, 21 contributed data to the all three testing stages. Thus, inter-individual differences other than sputum culture status may have contributed to the differences in costs observed.

Additionally, for patients considered cured, there were relatively few person-months of observation data available. Therefore the cost per month while cured may be overestimated and substantially lessen with a longer observation window following cure.

A benefit of pooling the data across the four countries was the increased person-time available for analysis; however, some differences in resource utilization trends were evident across jurisdictions. Consequently, trends in component costs were considered less reliable in the pooled analysis; however, the trend in overall costs over the course of NTMPD was thought to be strengthened.

Conclusion

Managing patients with negative sputum culture or those cured of NTMPD caused by MAC is likely to be associated with lower overall costs compared to managing patients with positive sputum culture. Improving treatment success rates in these patients could thus translate into substantial cost savings.

Disclosures

Ben Wilson, Sarah Goring, Nancy Risebrough, and Janice Watch are employees of ICONplc; Jack R Gallagher, Kylee J Heap and Susan Carroll are employees of Clarity Pharma Research LLC. Marko Obradovic is an employee of Insmed Germany GmbH. This research was funded by Insmed Incorporated (Bridgewater, NJ).

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