Diagnosis of tuberculosis among patients with unexplained pleural effusion in Belarus: role of surgical biopsy and Xpert MTB/RIF

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ABSTRACT

Introduction. Diagnosis of pleural tuberculosis is challenging, particularly in settings with high burdens of drug resistance. We examined the diagnostic yield of surgical biopsy and accuracy of Xpert MTB/RIF using pleural fluid and biopsy samples among patients with unexplained pleural effusion in Belarus. The Xpert MTB/RIF assay is fully automated cartridge-based real-time DNA-based test that can detect both tuberculosis (TB) and resistance to rifampicin in less than two hours. Xpert MTB/RIF is an automated polymerase chain reaction (PCR) test (that is, a molecular test) utilizing the GeneXpert platform (Cepheid; Sunnyvale, California, United States).

Methods. We tested consecutive patients with unexplained pleural effusion with pleural fluid microbiology, along with pleural biopsy histology and microbiology (2002–2018). A subset was also tested using Xpert MTB/RIF on pleural fluid and biopsy samples. We used a composite gold standard for TB, incorporating biopsy culture and histology results.

Results. Among 782 patients, 334 (42.7%) had a diagnosis of TB, of whom 61/232 (26.3%) with known drug susceptibility were multidrug-resistant. Most cases (54.8%) had microbiological and histological evidence of TB from pleural biopsy specimens. Sensitivities of Xpert MTB/RIF for pleural TB and rifampicin-resistant TB (RR-TB) were higher for pleural tissue than fluid (58.7% for pleural TB and 66.7% for RR-TB versus 20.5% and 16.7%, respectively). The specificity of Xpert MTB/RIF on pleural biopsy was 92.1% for TB, and 100% for RR-TB. While TB and RR-TB diagnoses took a median of 6.5 and 31 days, respectively, using conventional diagnostics, Xpert MTB/RIF results were available within one day.

Conclusion. Surgical biopsy plays an important role in the diagnosis of pleural TB in Belarus. Xpert MTB/RIF on pleural biopsy samples has higher sensitivity than on pleural fluid and may help expedite the diagnosis of TB and RR-TB in up to 60% of patients.

Keywords: PLEURAL BIOPSY, XPERT MTB/RIF, PLEURAL FLUID, PLEURAL TUBERCULOSIS, MULTIDRUG-RESISTANT TUBERCULOSIS, BELARUS

INTRODUCTION

Extrapulmonary tuberculosis (EPTB) represented 14% of the 6.4 million reported cases in 2017, ranging from 8% to 24%, according to the WHO Global Tuberculosis Report 2018 (1). Pleural TB represents one of the most frequent clinical forms of EPTB (2, 3). The diagnosis is made challenging by the low mycobacterial load in pleural fluid and the absence of pulmonary involvement in most cases, leading to a low diagnostic yield from sputum-based diagnostics due to the absence of infectious agents in sputum. Invasive procedures may therefore be carried out to obtain diagnostic specimens with risks of complications to patients (4–6).

In recent years, Xpert MTB/RIF has been introduced globally for the purpose of diagnosing pulmonary and extrapulmonary TB, including pleural TB (7). Studies conducted in other regions have demonstrated varying performance (sensitivity: 31–97%; specificity: 92–99%) for non-sputum specimens (8–12). For pleural TB, it is recommended that assessments of Xpert...
MTB/RIF performance use a composite gold standard, incorporating both microbiology and histology results (12). However, only one previous study has compared Xpert MTB/RIF performance to a composite gold standard using pleural biopsy samples (5).

Belarus has the highest prevalence of multidrug-resistance among new and retreatment TB cases globally. While the overall TB incidence rate is 37/100 000, 38% of new cases and 67% of retreatment cases are rifampicin-resistant (RR) or multidrug-resistant (MDR) (1). This high burden of drug resistance makes it imperative to attempt to microbiologically confirm TB cases and to obtain drug susceptibility testing. However, there are no data on the additional diagnostic yield of invasive surgical pleural biopsy (compared to pleural fluid sampling) for pleural TB in Belarus or describing the performance of rapid TB diagnostic methods (Xpert MTB/RIF) of pleural fluid and pleural biopsy specimens for TB and MDR-TB.

This study aimed to optimize the existing diagnostic algorithm for pleural TB in countries with high MDR-TB burdens, since expediting diagnosis may lead to timely treatment initiation and improved outcomes. Specifically, we sought to explore the additional diagnostic yield of surgery for pleural TB, and to evaluate the diagnostic accuracy of Xpert MTB/RIF using pleural fluid and pleural biopsy specimens, compared to a robust composite gold standard.

METHODS

DESIGN
This is a cross-sectional retrospective (2002–2018) study.

SETTING
Belarus is a middle-income European country with a population of 9.5 million, of whom over 70% reside in urban areas. The health care system in Belarus is funded largely through government taxation. The WHO DOTS (Directly Observed Treatment, Short-course) strategy was adopted in Belarus in 2001 and by 2005 its implementation was expanded to cover the entire country. TB detection and treatment are delivered with the support of dedicated TB care health care facilities and primary health care services. Patients with presumptive TB are usually evaluated at primary health care facilities or polyclinics. From these centres sputum specimens are transported to regional reference laboratories for direct smear microscopy and other tests. This research was conducted at the Republican Scientific and Practical Centre of Pulmonology and Tuberculosis of Belarus in Minsk.

PARTICIPANTS
Consecutive patients referred from other centres for further investigation of unexplained pleural effusions in the years 2002–2018 were included. Patients underwent pleural fluid sampling and surgical pleural biopsy. Pleural fluid and biopsy samples were sent to the National Reference Laboratory for microbiological investigations (microscopy, solid and liquid culture), while pleural biopsy samples were processed by the pathology laboratory of the Republican Scientific and Practical Centre of Pulmonology and Tuberculosis (Minsk, Belarus). For patients recruited from 2013 to 2018, Xpert MTB/RIF was also performed on both pleural fluid and pleural biopsy samples.

DATA VARIABLES
For each participant data were collected directly from their medical records concerning age, sex, history of TB contact, HIV status, occupational history and test results. We determined the participants’ final diagnoses using a composite gold standard for TB of either positive culture (solid or liquid) for Mycobacterium tuberculosis or histology compatible with tuberculosis. Double entry validation was used for data entry.

STATISTICAL ANALYSIS
Descriptive statistics (mean, proportion and median) were calculated. Comparisons between groups were performed using the Mann-Whitney U test or the chi-square test, where appropriate. Multivariate logistic regression was used to examine adjusted odds ratios for final diagnosis of TB among the study participants. Levels of significance were set at 5%.

The diagnostic accuracy of Xpert MTB/RIF in detecting Mycobacterium tuberculosis was tested against our composite gold standard for TB (12). Diagnostic accuracy of Xpert MTB/RIF in detecting rifampicin-resistance was tested among patients with culture-positive TB against the gold standard of phenotypic DST. For patients with drug-sensitive TB, time to diagnosis was compared between Xpert MTB/RIF and the earliest result (histology or microbiology) consistent with TB. For patients with MDR-TB, time to diagnosis was compared between Xpert MTB/RIF and the earliest result (phenotypic DST or LPA) consistent with MDR-TB. The database was stored in Microsoft Excel and analyses were performed using Stata version 15.0 (College Station, Texas, USA).

ETHICS
Permission to carry out the study was obtained from the Local Ethical Committee of the Republican Scientific and Practical Centre of Pulmonology and Tuberculosis of the Ministry of Health Care of Belarus. An ethics exemption was also obtained from the WHO Research Ethics Review Committee.
RESULTS

PARTICIPANT CHARACTERISTICS
A total of 782 consecutive patients with unexplained pleural effusion were included in the study. Baseline characteristics of the participants are shown in Table 1. Pleural fluid microbiologic analyses were conducted in 687/782 cases (87.9%). Pleural biopsy specimen microbiology analyses were performed in 755/782 cases (96.6%). Histology results of pleural biopsy specimens were available for 782/782 (100%) patients.

ETIOLOGY OF PLEURAL EFFUSIONS
TB was the final diagnosis in 334/782 patients (42.7%). Nonspecific causes of pleural effusion were established in 379/782 cases of patients (48.5%), while malignancies caused 69/782 (8.8%) cases. In 102 TB patients, we were unable to establish drug susceptibility. Among TB cases identified with known DST, 61/232 (26.3%) were MDR.

In the multivariate analysis (Table 1), only younger age (odds ratio (OR) 0.94; 95% confidence interval (CI) 0.92–0.95; p<0.001), history of TB contact (OR 3.24; 95% CI 1.95–5.37; p<0.001) and HIV infection (OR 5.17; 95% CI 1.07–25.07; p=0.04) were associated with a final diagnosis of TB.

DIAGNOSTIC YIELD OF PLEURAL FLUID AND PLEURAL BIOPSY
Figure 1 shows the proportion of TB cases diagnosed by pleural fluid microbiology (81/334; 24.3%), pleural biopsy microbiology (259/334; 77.5%) and pleural biopsy histology (315/334; 94.3%), respectively.

In 67/334 (20.1%) cases, the diagnosis of TB was obtained using all three methods. A total of 183/334 (54.8%) of diagnoses were made with both pleural biopsy microbiologic and histologic analyses. For 61/334 patients (18.3%), the diagnosis of pleural TB was made only by pleural biopsy histology.

### TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY COHORT (PATIENTS WITH PLEURAL EFFUSION IN BELARUS, 2002–2018), STRATIFIED BY FINAL DIAGNOSIS

<table>
<thead>
<tr>
<th></th>
<th>No TB</th>
<th>TB</th>
<th>Total</th>
<th>Odds ratio</th>
<th>p</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Median (IQR)</td>
<td>50 (40–57)</td>
<td>36 (27–46)</td>
<td>44 (33–54)</td>
<td>0.93 (0.92–0.95)</td>
<td>&lt;0.001</td>
<td>0.94 (0.92–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>126 (28.1)</td>
<td>112 (33.5)</td>
<td>238 (30.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>322 (71.9)</td>
<td>222 (66.5)</td>
<td>544 (69.6)</td>
<td>0.78 (0.57–1.05)</td>
<td>0.10</td>
<td>0.8 (0.54–1.19)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Health care worker</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No</td>
<td>377 (84.2)</td>
<td>275 (82.3)</td>
<td>652 (83.4)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>13 (2.9)</td>
<td>19 (5.7)</td>
<td>32 (4.1)</td>
<td>2 (0.97–4.13)</td>
<td>0.06</td>
<td>1.67 (0.71–3.92)</td>
<td>0.24</td>
</tr>
<tr>
<td>Missing</td>
<td>58 (12.9)</td>
<td>40 (12)</td>
<td>98 (12.5)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>TB contact</strong></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>392 (87.5)</td>
<td>250 (74.9)</td>
<td>642 (82.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41 (9.2)</td>
<td>68 (20.4)</td>
<td>109 (13.9)</td>
<td>2.6 (1.71–3.95)</td>
<td>&lt;0.001</td>
<td>3.24 (1.95–5.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing</td>
<td>15 (3.3)</td>
<td>16 (4.8)</td>
<td>31 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>HIV</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>383 (85.5)</td>
<td>275 (82.3)</td>
<td>658 (84.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (0.4)</td>
<td>11 (3.3)</td>
<td>13 (1.7)</td>
<td>7.66 (1.68–34.83)</td>
<td>0.01</td>
<td>5.17 (1.07–25.07)</td>
<td>0.04</td>
</tr>
<tr>
<td>Missing</td>
<td>63 (14.1)</td>
<td>48 (14.4)</td>
<td>111 (14.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>448 (100)</td>
<td>334 (100)</td>
<td>782 (100)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: TB – tuberculosis
IQR – interquartile range
HIV – human immunodeficiency virus

Note: Univariate and multivariate logistic regression analyses show risk factors for pleural tuberculosis. Data presented as n (%) or median (IQR) where indicated.
DIAGNOSTIC ACCURACY OF XPERT MTB/RIF

A total of 109 patients were included in our assessment of diagnostic accuracy of Xpert MTB/RIF for TB and drug-resistant TB in pleural fluid and pleural biopsy specimens (Table 2). The sensitivity of Xpert MTB/RIF for pleural fluid in our study cohort was 20.5% (95% CI 9.8–35.3) for diagnosis of TB. Among those with culture-confirmed TB with available DST results, the sensitivity was 16.7% (0.4–64.1) for RR-TB. The specificity of pleural fluid Xpert MTB/RIF was 100% for both TB and RR-TB diagnoses.

For pleural biopsy specimens, the sensitivity and specificity of Xpert MTB/RIF for TB diagnosis were 58.7% (43.2–73) and 92.1% (82.4–97.4), respectively. Among those with culture-confirmed TB with available DST results, the sensitivity was 66.7% (22.3–95.7) for diagnosing RR-TB, while the specificity was 96.2% (80.4–99.9).

The median times from sample collection to first TB and RR-TB diagnoses were 6.5 (5–8.5) and 31 (13–55) days, respectively, without Xpert MTB/RIF results (Table 3). For those with positive Xpert MTB/RIF, results were available within one day.

FIGURE 1. VENN DIAGRAM SHOWING DIAGNOSTIC YIELD OF DIFFERENT SPECIMENS AND LABORATORY METHODS FOR PLEURAL TUBERCULOSIS DIAGNOSIS IN BELARUS IN 2002–2018

DISCUSSION

STATEMENT OF PRINCIPAL FINDINGS

This study describes the burden and characteristics of pleural TB in Belarus in the years 2002–2018. To our knowledge, this is the first study to describe the etiology of pleural effusions in Belarus and to report the yield of surgical biopsy. Our data show that TB accounts for a large proportion of unexplained pleural effusions in Belarus (42.7%), of which 26.3% are MDR-TB. TB was more common among patients of younger age, with a known history of TB contact, and with HIV-positive status.

We found that surgical pleural biopsy played a crucial role in the diagnosis of pleural TB, since only 24.3% of TB cases could be identified using pleural fluid samples alone. The vast majority of diagnoses were obtained through a combination of microbiologic and histologic analyses of pleural biopsy specimens (54.8%), or through histology alone (18.3%). These data suggest that, despite the risk of complications to patients from invasive procedures, surgical biopsy is likely to be justified among patients with unexplained pleural effusion in settings with high TB incidence (6, 13, 14), and even more so in settings with high MDR-TB burdens, where obtaining a microbiological diagnosis is even more important.

This is also, to our knowledge, the first study reporting the performance of Xpert MTB/RIF using non-sputum samples in Belarus. We found that the sensitivity of Xpert MTB/RIF for pleural TB and drug-resistant TB was higher for pleural biopsy specimens than for pleural fluid (58.7% for pleural TB and 66.7% for RR-TB versus 20.5% and 16.7%, respectively). This is consistent with previous data (12). However, we found that the specificity of Xpert MTB/RIF for TB using pleural biopsy (92.1%) was lower than previously reported (5). This led to a reduced positive predictive value for TB of 84.4% (67.2–94.7). This suboptimal sensitivity was driven by five cases being classified as false-positive Xpert MTB/RIF results, compared to our composite gold standard. On review of these false-positive cases, two were malignancy, while three had nonspecific pleuritis. None of these five cases had a history of TB.

Importantly, we found a marked improvement in time to diagnosis of pleural TB and RR-TB with the addition of Xpert MTB/RIF in the diagnostic algorithm. With this method, we obtained the diagnosis of TB and RR-TB in one day after sample collection. In comparison, the median time to diagnosis using conventional diagnostics was 6.5 days for TB diagnosis, while DST results took a median of 31 days. These data suggest that, while Xpert MTB/RIF on pleural samples may not detect all pleural TB cases, the reduction in time to diagnosis for...
TABLE 2. DIAGNOSTIC ACCURACY OF XPERT MTB/RIF FOR PLEURAL TUBERCULOSIS IN STUDY COHORT (BELARUS, 2013–2018)

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>MDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pleural fluid</td>
<td>Pleural biopsy</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td><strong>n</strong></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td><strong>N</strong></td>
<td>44</td>
</tr>
<tr>
<td></td>
<td><strong>Estimate, %</strong></td>
<td>20.5 (9.8–35.3)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td><strong>n</strong></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td><strong>N</strong></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td><strong>Estimate, %</strong></td>
<td>100 (93.7–100)</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td><strong>n</strong></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td><strong>N</strong></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td><strong>Estimate, %</strong></td>
<td>100 (66.4–100)</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td><strong>n</strong></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td><strong>N</strong></td>
<td>92</td>
</tr>
<tr>
<td></td>
<td><strong>Estimate, %</strong></td>
<td>62 (51.2–71.9)</td>
</tr>
</tbody>
</table>

**Legend:**
- TB – tuberculosis
- MDR-TB – multidrug-resistant tuberculosis
- PPV – positive predictive value
- NPV – negative predictive value

TABLE 3. TIME TO DIAGNOSIS OF TB AND MDR-TB AMONG PATIENTS WITH PLEURAL EFFUSION IN BELARUS IN THE YEARS 2013–2018

<table>
<thead>
<tr>
<th></th>
<th>No Xpert MTB/RIF</th>
<th>Xpert MTB/RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days to TB diagnosis</strong></td>
<td>6.5 (5–8.5)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td><strong>Days to MDR-TB diagnosis</strong></td>
<td>31 (13–55)</td>
<td>1 (1–1)</td>
</tr>
</tbody>
</table>

**Legend:**
- IQR – interquartile range
- TB – tuberculosis
- MDR-TB – multidrug-resistant tuberculosis

A subgroup of patients detected by Xpert MTB/RIF could lead to expedited treatment initiation and subsequent improvement in individual outcomes.

**STRENGTHS AND WEAKNESSES OF THE STUDY**

The study was performed on a large number (782) of consecutively sampled patients with unexplained pleural effusion over a 17-year period, where 334 cases (42.7%) were diagnosed as TB cases. While the study was conducted at a single centre, it was a national referral centre. Therefore, we received referrals from all regions of Belarus, which makes our study population representative of the entire country. Our findings are thus likely to be generalizable to other eastern European countries with high burdens of drug-resistant TB. To minimize bias due to differing laboratory practices, all the
laboratory investigations took place in the same microbiology (National Reference Laboratory) and histology laboratories. Moreover, our study population was thoroughly investigated, with pleural fluid microbiology, pleural biopsy microbiology and histology results available for 87.9%, 96.6% and 100% of participants, respectively. This allowed us to implement a robust composite gold standard definition for TB, which significantly strengthens our diagnostic accuracy assessment of Xpert MTB/RIF. To put this in the context of the wider literature, this is only the second published study to assess Xpert MTB/RIF performance against a composite reference standard, and first from the European Region.

Our study is also subject to some limitations. Firstly, given the recent introduction of a newer Xpert Ultra cartridge, prospective assessments of the performance of the newer assay are needed. Secondly, we are unable to assess the etiology of pleural effusions among patients who were not referred for surgery and, therefore, did not reach our centre. This could have led to selection bias, with our sample potentially representing those among whom achieving a diagnosis was most challenging, leading to underestimation of the yield of pleural fluid. However, our results of the yield of pleural fluid analysis are reassuringly similar to previous data (6, 13, 14). Thirdly, DST data were unavailable for 102/334 patients, most of whom were culture-negative and diagnosed solely on histology. This limitation reflects the challenge of obtaining a microbiological diagnosis in pleural TB, even when surgical biopsy is performed. Fourthly, we did not evaluate the diagnostic accuracy of other non-microbiological tests on pleural fluid, such as adenosine deaminase or interferon-gamma, for pleural TB (15). However, the high burden of drug resistance in Belarus necessitates obtaining a microbiological diagnosis whenever possible. Therefore, the utility of these biomarkers is likely to be limited in our setting. Finally, we did not assess TB treatment outcomes in this cross-sectional study since its aim was to assess the diagnostic yield of surgical biopsy and accuracy of Xpert MTB/RIF for diagnosis of pleural TB. Treatment outcomes among patients with pleural TB in settings with high burdens of drug resistance may be addressed in future studies.

CONCLUSIONS: UNANSWERED QUESTIONS AND FUTURE RESEARCH

In summary, we have demonstrated that TB is common among patients with previously unexplained pleural effusion in Belarus, accounting for over 40% of cases. Only a quarter of these cases can be diagnosed using pleural fluid samples alone, which demonstrates the value of obtaining invasive pleural biopsy specimens in making a final diagnosis. We have also shown that Xpert MTB/RIF performance is significantly better for pleural biopsy specimens than for pleural fluid, achieving sensitivity approaching 60%. For patients detected by Xpert MTB/RIF, this leads to an expedited diagnosis, particularly for the subgroup with RR-TB. Further research is required to test whether Xpert Ultra leads to further improvements in performance, and to assess whether using Xpert MTB/RIF in the diagnostic algorithm leads to improved individual patient outcomes.

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Conflicts of interest: None declared.

Disclaimer: The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization.

REFERENCES


1 All references were accessed 13 December 2019.


