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REVIEW ARTICLE

Microscopy compared to culture for the diagnosis of tuberculosis in induced sputum samples: a systematic review

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SUMMARY

BACKGROUND: Resource-limited settings rely on sputum examination using microscopy to diagnose tuberculosis (TB); however, the sensitivity of the test is poor and case detection rates are low. Sputum induction is proposed as a way to improve sample collection and enhance test sensitivity.

OBJECTIVE: To undertake a systematic review of studies comparing microscopy and culture sensitivity in induced sputum samples.

METHODS: We ran duplicate searches of databases (up to August 2011) and searchable websites of major human immunodeficiency virus (HIV) and TB conferences (up to November 2010) to identify studies comparing the performance of microscopy compared to culture on induced sputum samples, with culture as the reference standard.

RESULTS: A total of 23 studies met our inclusion criteria. The overall success of the induction was high, ranging from 76.4% (95%CI 68.5–83.2) to 100% (95%CI 98.5–100), while adverse events associated with sputum induction were infrequent and mild. The sensitivity of microscopy compared to culture ranged from 0% to 100%; only eight studies reported on the species of mycobacterium isolated in culture. Yield was generally higher for sputum induction compared to nasopharyngeal aspiration and gastric lavage, and compared equally well to bronchoalveolar lavage and physiotherapy.

DISCUSSION: Sputum induction increases TB case detection and is useful for people who are negative on spontaneous smear microscopy or unable to expectorate spontaneously. It is well-tolerated by children and adults, irrespective of HIV status, and can be used where culture is not available. The use of induced sputum samples with molecular tests, such as Xpert® MTB/RIF, warrants further investigation.

KEY WORDS: sputum induction; tuberculosis; microscopy; culture; sensitivity

IN 2010, there were an estimated 12 million prevalent tuberculosis (TB) cases worldwide and 8.8 million incident cases, resulting in 1.45 million deaths, including 0.35 million in persons co-infected with the human immunodeficiency virus (HIV). Case detection rates remain poor, particularly in the World Health Organization (WHO) Africa Region where only 60% of estimated incident cases were detected and notified during 2010.[1] Globally, 6.2 million TB cases were notified during 2010, of which 75% (4.6 million) were new pulmonary cases. Delayed diagnosis is detrimental to patient outcomes,[2] and untreated infectious pulmonary disease leads to further disease transmission.[3]

Pulmonary TB is commonly diagnosed by microscopic examination of spontaneously expectorated sputum. It is not a sensitive technique, and only 57% of notified new pulmonary cases in 2010 were smear-positive.[1] In the absence of alternative diagnostic tests, smear-negative cases may remain undetected and unreported, contributing to the burden of untreated infectious disease.

Smear microscopy has reported sensitivities ranging from 61.8% to 70% when compared to culture.[4–6] However, the HIV epidemic has led to a substantial increase in the frequency of smear-negative pulmonary TB,[7] and sensitivities of below 30% are reported in parts of Africa where HIV prevalence is high.[8] Microscopy relies on the production of purulent sputum samples, but quality varies: one study, from Indonesia, found that only a third of TB suspects who had undergone TB diagnosis provided at least one good sample, and less than one in seven were able to provide three good quality samples;[9] this may vary depending on the patient characteristics.[10] Samples that contain mainly saliva rather than bronchial expectoration rarely contain mycobacteria, and are of reduced value for TB diagnosis.[11]

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Sputum induction is frequently proposed as a technique to improve sample collection, and has been found to be relatively easy to perform and generally well tolerated.[12–15] The technique involves using sterile water or hypertonic saline to irritate the airways, which promotes coughing and production of a specimen. While sputum induction does not require high levels of technology or training, its utility at the peripheral level is limited by the fact that culture is usually only available at national reference laboratories. If microscopy could be used instead of culture this would improve the utility of sputum induction in such settings. However, the usefulness of sputum induction for TB diagnosis is unclear: studies reporting similar results have concluded that sputum induction had no added value over spontaneous expectoration,[16] or that induction was a useful and cost-effective intervention.[17]

We undertook a systematic review of studies assessing the performance of microscopy compared to culture in induced sputum samples. Culture of induced sputum was taken as the reference standard.

METHODS

Search strategy

We developed a search strategy combining key terms that may indicate sputum induction (sputum induction, induced sputum, sputum expect* and sputum sampl*) with TB. The following databases were searched from inception up to August 2011: PubMed, Embase, the Web of Science and Google Scholar. We also searched abstracts of the following conferences: all electronic abstract books of the Union World Conferences on Lung Health conferences (up to Berlin, November 2010), the Society of General Microbiology (up to Nottingham, September 2010), the American Society of Tropical Medicine (up to Washington 2009) and all International AIDS Society conferences (up to Vienna, July 2010) and all Conferences on Retroviruses and Opportunistic Infections (up to San Francisco, February 2010). Our search was complemented by reviewing the bibliographies of relevant papers. No language restriction was applied. Where needed, authors of original studies were contacted for additional information.

Study selection and data extraction

One of the authors (PH) scanned all articles by title and abstract for initial inclusion according to predefined inclusion criteria. We included any studies investigating the use of sputum induction for the diagnosis of pulmonary TB, regardless of age, HIV status or presence or absence of symptoms. Studies were excluded if they did not provide separate results for microscopy and culture for comparison. Final inclusion of potentially eligible articles was assessed in duplicate (PH, NF). Data extraction was done in duplicate (PH, NF) using pre-defined extraction tables to collect information about study characteristics. We extracted data on culture and microscopy results for all sputum collection methods. We defined a positive result as one or more positive smears or culture, irrespective of how many samples were processed per patient. The methodological quality of studies was assessed using a framework adapted from the Cochrane handbook for the systematic review of diagnostic test accuracy.[18]

Data analysis

We assessed inter-rater reliability on inclusion of articles by calculating the φ statistic. We calculated point estimates and 95% confidence intervals (CIs) for the sensitivity of microscopy compared to culture. All P values were two-sided, and $P < 0.05$ was considered significant. All analyses were conducted using Stata version 11 (Stata Corp, College Station, TX, USA). NF and PH conducted all statistical analyses.

RESULTS

Our initial search identified 668 abstracts (Figure 1): 42 studies met the inclusion criteria for assessment of full articles, and 23 studies (3127 participants) were included for analysis. Agreement on final inclusion was high ($\varphi = 0.92$). Nineteen studies were excluded

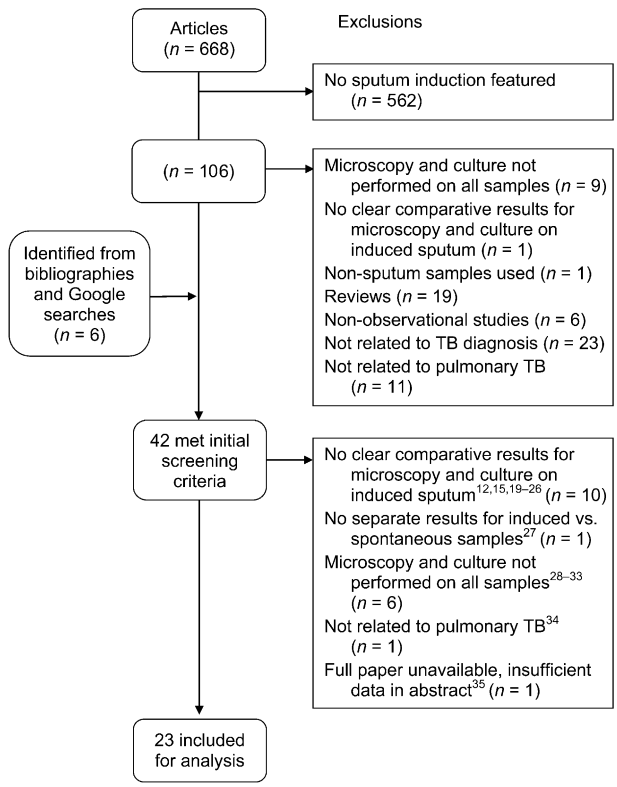

Figure 1 Flow diagram of study selection process.

for the following reasons: 10 had no clear comparative results for microscopy and culture on induced sputum;[12,15,19–26] 1 had no separate results for induced vs. spontaneous samples;[27] for 6 studies, microscopy and culture were not performed on all samples;[28–33] 1 study was not related to pulmonary TB,[34] and for 1 study, the full paper was unavailable, in spite of attempts to contact the authors.[35]

Heterogeneity among studies

Study characteristics are summarised in the Table. Ten studies were carried out in Africa,[36–45] 5 in Asia,[13,46–49] 4 in the Americas[16,50–52] and 4 in Europe.[14,17,53,54] The majority of the studies included HIV-positive patients: 13 had mixed HIV-positive and -negative populations,[14,16,36,37,39–42,44,45,50,51,53] two included only HIV-positive patients,[43,52] one included only HIV-negative patients,[48] and the remainder did not report HIV status.[13,17,38,46,47,49,54] Fifteen studies were conducted exclusively among adults,[13,14,37,41–43,45,47–54] six exclusively among children,[36,38–40,42,44,46] one included both children and adults,[17] and one did not state age.[16]

Most studies (20/23) selected patients based on clinical suspicion of TB infection.[13,14,17,36–39,41–50,52–54] One also included HIV-positive patients, regardless of symptoms.[45] Seven studies used radiology to confirm suspicion,[13,14,42,46–48,54] 10 recruited patients who were unable to expectorate spontaneously,[14,17,37,42,43,47–50,53] and 7 recruited patients who had had smear-negative microscopy results following spontaneous expectoration.[37,41–43,48,50,53] Sixteen studies were prospective cohort studies,[13,14,17,37,40–46,48,50–53] 4 were cross-sectional studies,[36,38,47,49] 2 were prospective multicentric cohorts,[39,54] and 1 was a retrospective review.[16]

Ultrasonic nebulisers were used in 15 studies,[14,17,37,38,41–43,45,47–51,53,54] 4 used jet nebulisers,[16,39,40,45] 1 used a Venturi-type face mask nebuliser,[17] 3 used other techniques,[13,46,52] and 2 did not state type of nebuliser.[36,44] Sputum induction was the only sampling method investigated in 12 studies.[13,16,17,36–38,44,45,47,50,51,53] Six studies also investigated gastric lavage,[14,39–41,46,49] 2 investigated fibreoptic bronchoscopy,[48,54] 1 investigated nasopharyngeal aspiration,[46] 2 investigated bronchoalveolar lavage (BAL),[14,41] and 2 investigated physiotherapy (Table 1).[41,52] One study also investigated the string test and blood culture,[42] while another study performed culture of extra-pulmonary samples as appropriate.[43]

Of 23 studies, 3 used direct Ziehl-Neelsen (ZN) microscopy,[13,37,46] 1 used concentrated ZN microscopy,[41] 1 used direct fluorescent microscopy,[38] 7 used concentrated fluorescent microscopy,[14,39,40,42,44,45,50] 8 used ZN or Kinyoun microscopy where use of sputum concentration was not stated,[16,36,38,47–49,52,54] and 4 used fluorescent microscopy where use of sputum concentration was not stated.[17,43,51,53] Thirteen studies exclusively used solid media (Löwenstein-Jensen, Middlebrook, Ogawa or a combination),[13,17,36–38,41,42,46–49,51,52] 5 exclusively used liquid media (BACTEC™, BacT/ALERT® or Mycobacteria Growth Indicator Tube),[14,39,40,44,45] and 3 used a combination of liquid and solid media.[43,50,54] The remainder did not state the culture media used.[16,53] Half (11/23) collected one sample,[13,17,36,38,40–42,47,49,52,53] and the remainder collected multiple samples.[14,16,37,39,43,44–46,50,51,54] Two studies collected 1 sample per type of nebuliser assessed,[17,45] and 1 study did not clearly state the number of samples collected.[48]

Study outcomes

The success of the induction procedure could be calculated for all but one study.[16] Overall, success was high, ranging from 76.4% (95%CI 68.5–83.2) to 100% (95%CI 98.5–100). Adverse events associated with sputum induction were infrequent and mild, and included cough,[13,39,40] nausea,[13,17] vomiting,[42] epistaxis, coughing, wheezing and vomiting,[39,40] and nose bleeds, vomiting, increased cough and wheezing.[44] Four studies reported that there were no adverse events.[37,38,45,48] Eleven studies did not report adverse events (Appendix).[16,36,42,43,46,47,50–54]*

Positivity rates ranged from 0% (95%CI 0–13.7) to 41.8% (95%CI 28.7–55.9) for microscopy smears, and from 2.4% (95%CI 1.1–4.5) to 100% (95%CI 85.8–100) for cultures. These estimates are primarily dependent on background TB prevalence rather than method of assessment. Among those patients who had previously been found negative on spontaneous smear microscopy, or who had not been able to expectorate, microscopy positivity rates ranged from 2% to 41.8%.[37,41–43,48–50,53]

The sensitivity of microscopy compared to culture ranged from 0% (95%CI 0–26.5)[47] to 100%.[44] These results are summarised in Figure 2. (Note that for one study, more patients were found to be positive on microscopy than culture; as confidence intervals could not be generated, this study is not represented).[44] Three studies reported smear-positive, culture-negative samples: one study reported that one sample that was positive on microscopy was negative on culture,[38] another stated that sputum samples from four children were microscopy-positive and culture-negative,[39] and a third reported that no smear-positive samples were culture-positive, and no culture-positive samples were smear-positive.[44] Eight of 23 studies investigated the species of mycobacteria discovered. Two studies reported that 100% of species found were *Mycobacterium tuberculosis* complex,[37,44] and two more that speciation had been performed, and did not describe the isolation of non-tuberculous mycobacteria (NTM).[43,45] One study isolated NTM, but excluded these patients from the study.[47] Another

* The Appendix is available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2012/00000016/00000005/art00005

Table Characteristics of included studies

Study	Country	Year	Study type	Age	HIV status *n/N*	Selection criteria	Sample size*	Samples per patient	Type of nebuliser	Comparison with other sampling methods
Al-Aghbari[46]	Yemen	2003–2005	Prospective cohort	Children; median: 5 years	NS	Clinical suspicion of PTB, including radiological suspicion	88	1–3	Salbutamol via metered dose inhaler and oxygen	Nasopharyngeal aspiration and gastric aspiration
Al Zahrani[50]	Canada	1995–1998	Prospective cohort	Adults; mean: 44 years†	2/60 HIV+ (3.3%)	Clinical suspicion of PTB; spontaneous smear-negative or unable to expectorate spontaneously	503	>1	Ultrasonic	None
Atiq-ur-Rehman[13]	Pakistan	2006	Prospective cohort	Adults; mean: 34.3 years	NS	Strong clinical and radiological suspicion of PTB	164	1	Compressor	None
Bell[41]	Malawi	2005–2006	Prospective cohort	Adults; mean: 36 years	75/111 HIV+ (89%)	Clinical diagnosis of smear-negative PTB	111	1	Ultrasonic	Physiotherapy, gastric washing and BAL
Breen[53]	United Kingdom	2005–2006	Prospective cohort	Adults; median: 32 years	16/42 HIV+ (38%)	Clinical suspicion of TB; spontaneous smear negative or unable to expectorate spontaneously	42	1	Ultrasonic	None
Brown[14]	United Kingdom	2004–2006	Prospective cohort	Adults; median: 28 years	3/84 HIV+ (3.6%)	Clinical suspicion of TB; unable to expectorate spontaneously, radiography suggestive of TB	127	5	Ultrasonic	Gastric washing/ aspiration and BAL
Iriso[36]	Uganda	NS	Cross-sectional	Children; mean: 25.5 months	62/126 HIV+ (49%)	Clinical suspicion of TB	101	1	NS	None
Kawada[49]	Japan	1994–1996	Cross-sectional	Adults; mean: 39 years	NS	Clinical suspicion of TB; unable to expectorate spontaneously	22	1	Ultrasonic	Gastric aspiration
Kawada[47]	Urban hospital, Japan	1996–1997	Cross-sectional	Adults; mean: 37 years	NS	Clinical suspicion of PTB, including radiological suspicion, unable to expectorate spontaneously	27	1	Ultrasonic	None
Klein[51]	Urban Teaching Hospital, USA	1990–1992	Prospective cohort	Adults; age not stated	251/373 HIV+ (67%)	Suspected *Pneumocystis carinii* pneumonia	373‡	1 or more	Ultrasonic	None
Kranzer[45]	South Africa	2010	Prospective cohort	Adults; median: 39 years	66/123 HIV+ (53.7%)	HIV+ or symptoms suggestive of TB infection	109	1 per nebuliser type	Ultrasonic and human-powered (jet)	None
Merrick[16]	Urban Teaching Hospital, USA	1989-1994	Retrospective review	NS	17/24 HIV+ (70.8%)	Patients with culture-positive TB	24	3	Jet	None
Moore[44]	Primary health care clinic, South Africa	2007–2009	Prospective cohort	Children; median: 38 months	48/270 HIV+ (18%)	Clinical suspicion of TB, adult household contact, or newly HIV-diagnosed with respiratory symptoms	270	2	NS	None

Morse[42]	Botswana	2006–2007	Prospective cohort	Adults; male range: 20–80 years; female range: 21–69 years	114/140 HIV+ (81.4%)	Clinical suspicion of TB, including radiological suspicion, unable to expectorate spontaneously or smear-negative on spontaneous expectoration	140	1	Ultrasonic	Urine culture, string test culture and blood culture
Parry[37]	Urban hospital, Malawi	NS	Prospective cohort	Adults; mean: 35 years	37/82 HIV+ (45.1%)	Clinical suspicion of TB, unable to expectorate spontaneously or smear-negative on spontaneous smear	82	1 to 3	Ultrasonic	None
Saglam[48]	Turkey	2001–2003	Prospective cohort	Adults; mean: 35.8 years	100% HIV−	Clinical suspicion of TB, including radiological suspicion; smear-negative on spontaneous expectoration or unable to expectorate spontaneously	55	Unclear	Ultrasonic	Fibreoptic bronchoscopy
Schoch[54]	Switzerland	2003–2005	Prospective cohort	Adults; mean: 38 years	NS	Asylum seekers with radiology suggestive of TB infection	91	2 (results presented are for second sample only)	Ultrasonic	Bronchoscopy
Shata[38]	Malawi	NS	Cross-sectional	Children; range: 3–15 years	NS	Clinical suspicion of TB infection	30	1	Ultrasonic	None
Souza Pinto[52]	Brazil	2004–2005	Prospective cohort	Adults; age not stated	100% HIV+	Adult clinical TB suspects, HIV+	132	1	Regular-flow oxygen	Chest physiotherapy
Toubes[17]	Spain	1997-2000	Prospective cohort	Adults and children; range: 7–90 years	NS	Active TB suspects, unable to expectorate spontaneously	90	1 sample per induction technique (results of both techniques combined)	Ultrasonic + Venturi-type face mask	None
Wilson[43]	South Africa	2002	Prospective cohort	Adults; age not stated	100% HIV+	Smear-negative TB suspects, unable to produce sputum or 2× spontaneous smear-negative	147	1–2	Ultrasonic	Culture of blood, urine and extra-pulmonary aspirates where appropriate
Zar[40]	South Africa	1998	Prospective cohort	Children; median: 9 months	100/142 HIV+ (70.4%)	Primary diagnosis of pneumonia; HIV+ or suspected positive; or admitted to ICU	149	1	Jet	Gastric lavage
Zar[39]	South Africa	2000–2002	Prospective cohort	Children; median: 13 months	95/250 HIV+ (38%)	Suspected pulmonary tuberculosis	250	3	Jet	Gastric lavage

* Sample size reported for cohort attempting sputum induction.
† Calculated.
‡ Final sample size (initial sample on which induction was attempted is unclear).
HIV = human immunodeficiency virus; NS = not stated; PTB = pulmonary TB; + = positive; TB = tuberculosis; − = negative; BAL = bronchoalveolar lavage; ICU = intensive care unit.

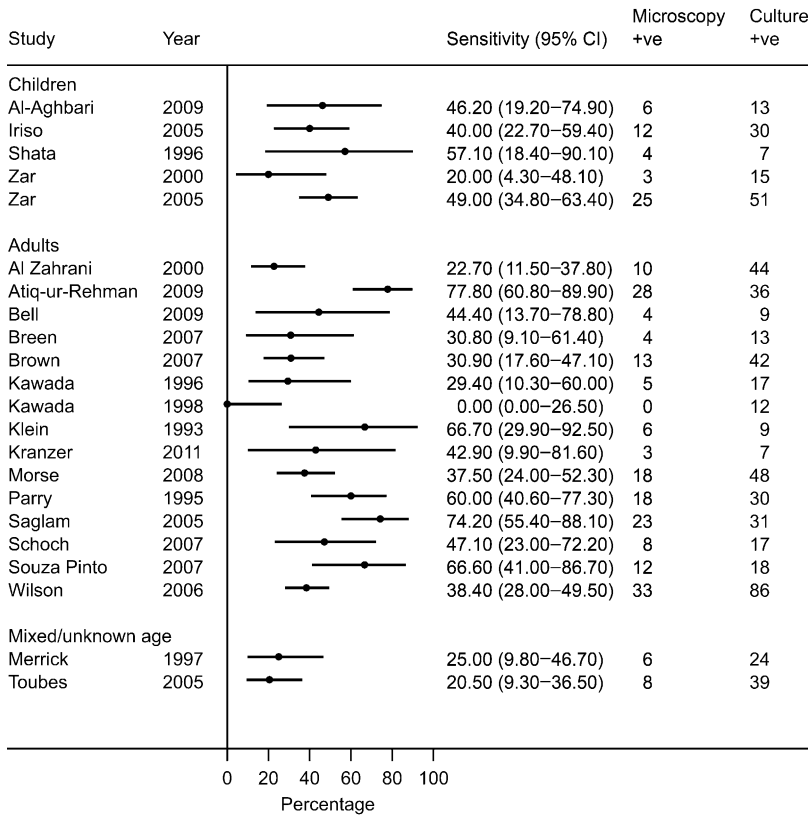

Figure 2 Forest plot summarising the sensitivity of microscopy compared to culture for induced sputum.

study reported that two microscopy smears (0.54%) were positive for *M. avium* complex and 64 cultures (17.2%) were positive for NTM.[51] A further two studies reported NTM cultures, but it was unclear if these were from induced sputum,[52] or included in the main analysis.[17]

Comparison with other sputum collection techniques

Eleven of 23 studies compared sputum induction with other sputum collection techniques. Six studies compared sputum induction with gastric aspiration: in three of these studies, the positivity rate for microscopy was the same for both techniques, while the sensitivity of microscopy compared to culture was higher for gastric aspiration,[14,40,46] and in three studies the microscopy positivity rate was higher for induced sputum, while sensitivity compared to culture was higher for sputum induction.[39,41,49] One study investigated use of nasopharyngeal aspiration, and the yield for both microscopy and culture was higher with nasopharyngeal aspiration, with the technique also showing a higher sensitivity for microscopy compared to culture.[46] BAL and fibreoptic bronchoscopy were compared with sputum induction in four studies. For two studies, the yield using culture and microscopy, as well as the sensitivity of microscopy in relation to culture, was higher on induced sputum.[14,54] One study showed higher yields from induced sputum for both microscopy and culture, yet the sensitivity for microscopy compared to culture was higher for BAL,[41] and another study had higher positivity rates on bronchoscopy for both microscopy and culture, as well as higher sensitivity for microscopy than culture.[48] Physiotherapy was investigated in two studies. In one study, positivity rates for microscopy, as well as sensitivity compared to culture, were higher from the chest physiotherapy sample, but positivity rates for culture were the same;[52] the second study had higher positivity rates on both microscopy and culture, as well as higher sensitivity for microscopy compared with culture, for chest physiotherapy samples.[41] Figure 3 summarises the sensitivity of microscopy compared to culture for those studies in which multiple sample collection techniques were assessed. Results from two studies reported sensitivities of over 100% (for lymph node biopsy,[43] and physiotherapy;[52] these studies are not represented in Figure 3).

Assessment of methodological quality

We assessed all full articles for methodological quality. All but one[51] studied a sample of patients that could be considered to be representative of the population who would undergo sputum induction for TB diagnosis in practice, and all but three[17,46,54] studies accounted for withdrawals; 9 studies provided a clear

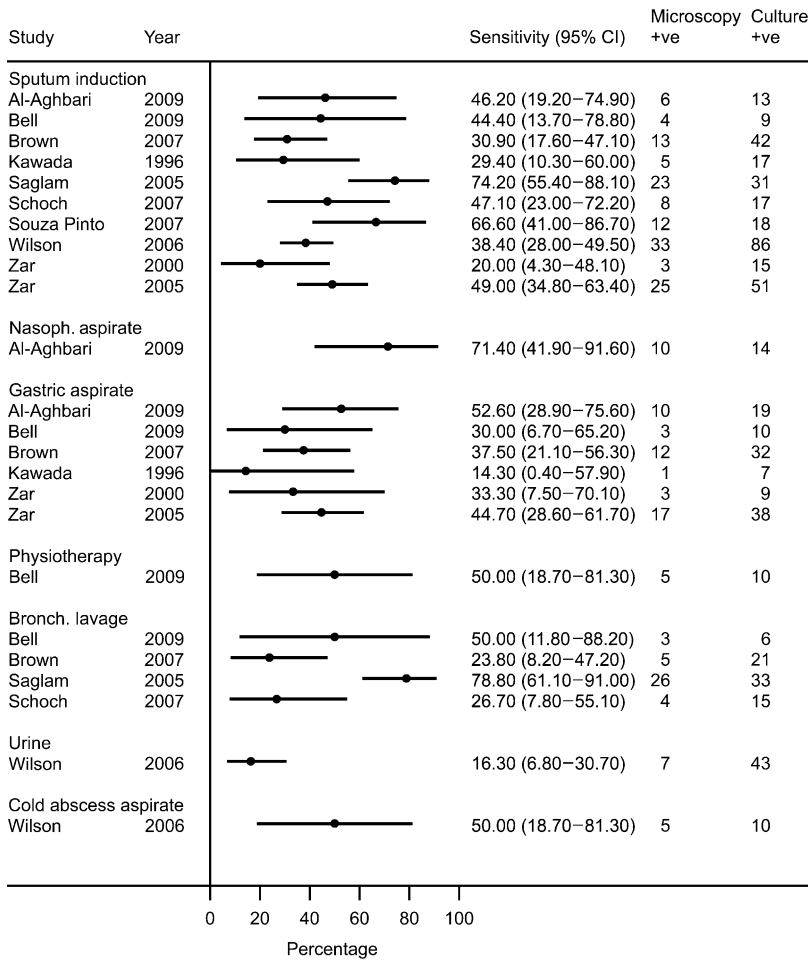

Figure 3 Forest plot summarising the sensitivity of microscopy compared to culture for studies comparing different sputum collection methods.

definition of what was considered to be a positive result.[16,17,39,40,42–44,50,53] Overall, we rated the methodological quality of the studies as adequate.

DISCUSSION

Improved detection of pulmonary TB is considered a priority by the World Health Organization and the Stop TB Partnership. The current frontline diagnostic test, smear microscopy, lacks sensitivity. Case finding might be augmented through the implementation of sputum induction to improve the quality of samples examined. Our systematic review of the published data found that the success of sputum induction was high across a range of study settings and patient groups.

Studies used both ZN and fluorescent microscopy. Fluorescent microscopy has been found to be more sensitive than ZN microscopy, but it can also be prone to lower specificity due to the appearance of artifacts.[55] Both solid and liquid culture was performed. Liquid culture is known to be more sensitive than solid, but it is also more prone to contamination and to grow NTM.[56] Due to the slow growth of *M. tuberculosis* and the sophisticated laboratory facilities required, culture is rarely available as a diagnostic option in high-burden countries.

The overall success rate for induction was high, with no important difference between patient groups of study settings, implying that the procedure is worth implementing in diverse settings where patients find spontaneous expectoration difficult. Sputum induction is potentially highly beneficial for HIV-positive patients, as they commonly have problems expectorating spontaneously and sputum smear microscopy is known to be less sensitive in this patient population. Results were similar for studies that included children, another group for whom sputum expectoration may be difficult. Good results were found among people who were spontaneous smear-negative or who were unable to expectorate. The procedure was well tolerated, with most studies reporting only mild and infrequent side-effects. Epistaxis, reported by two paediatric studies, should be carefully considered as it poses an infection risk to health care workers, particularly in high HIV prevalence settings. Because sputum induction induces coughing, which generates micro-aerosols, it has been recommended that it

should only be performed when spontaneous expectoration has failed, and using exhaust ventilation devices, with health care workers using respiratory protection.[57] Guidelines for resource-limited settings recommend optimising natural ventilation in places where sputum induction is performed.[58]

The sensitivity of microscopy on induced sputum compared to culture varied considerably across studies, with no clear influence of study setting or patient population. Although sensitivity was low, it allows for a more accurate diagnosis compared to the use of non-specific clinical diagnostic algorithms that are often the only alternative at peripheral health centres in resource-limited settings where culture facilities are not available or difficult to access. The sensitivity reported by some studies for microscopy compared to culture is similar to sensitivity for direct smear microscopy, and thus implies that it is worth implementing when only microscopy can be performed. Patients with negative results can be reassessed following a diagnostic algorithm. On-site testing also reduces loss to follow-up that can result when samples are referred to a central laboratory for further investigation.

We did not find any important difference in yield when comparing studies in which single or multiple sampling was done, which is an important consideration for resource-limited settings, as single sampling reduces processing time and cost. This would also facilitate same-day diagnosis, in line with the proposed move to same-day sample collection and microscopy to replace sample collection on consecutive days.[59]

The other sampling techniques evaluated in these studies mostly resulted in lower positivity rates than sputum induction. Notably, physiotherapy resulted in the same yield as sputum induction in one study; this merits further investigation—physiotherapy is an intervention that may be of particular use in resource-limited settings as it does not require expensive equipment or intensive training. However, the overall performance of these different techniques could not be assessed due to insufficient reporting of specificity data.

Strengths of this review include an extensive search strategy that identified 23 studies reporting our primary outcome, and analytical approaches to assess differences between study and patient characteristics. We described potential sources of heterogeneity, but were unable to provide pooled estimates, as very few studies reported specificity, which limited our ability to account for the trade-off between sensitivity and specificity required for more robust assessments of diagnostic accuracy.[60] The sensitivity of spontaneous smear microscopy can be affected by numerous factors, including sputum quality, smear preparation, staining procedures, examination time and the amount of training received in accurate smear examination, but too few studies reported this information for it to be formally assessed. Finally, all systematic reviews are subject to potential publication bias. However, the determinants and extent of publication bias for diagnostic studies is unclear, and because statistical tests are not generally applicable,[18] this was not formally assessed.

A potential limitation is the use of strict exclusion criteria, which led to the exclusion of some large-scale studies.[15,19,20,28] The question being researched by this review involved the comparison of microscopy yields on induced sputum compared with culture yields. As such, studies had to demonstrate clear and comparable data for yields on microscopy and culture to be included.

Our systematic review highlights several areas for future research. In particular, future research should report the proportion of microscopy-positive and culture-negative samples, as well as the species of mycobacteria isolated so that conclusions on the accuracy of induced sputum can be made. The performance of sputum induction compared to other techniques merits further assessment. Further research is also warranted to determine the optimal combination of nebuliser and saline concentrations, as this varies considerably between studies. Finally, the use of induced sputum in newer tests such as the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) should be vaildated.[61,62]

In conclusion, sputum induction can be useful when implemented for use with smear microscopy for people who are negative on spontaneous smear microscopy or who are unable to expectorate spontaneously, and is well-tolerated by children and adults alike. Induction procedures have a high success rate. As it is a cough-generating procedure, biosafety issues must be carefully considered prior to implementation. The technique requires less infrastructure than that required for culture facilities, and as such can potentially be implemented for use with microscopy in peripheral areas. However, most studies were not performed in peripheral settings, and further research is required to determine the applicability of sputum induction to such settings, although initial evidence of implementation in resource-limited settings is promising.[44]

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Appendix Study outcomes

			Success of sputum induction			Positivity rate		Sensitivity (microscopy vs. culture)		
Study	Microscopy method	Culture method	Successfully induced *n/N*, % (95%CI)	Reasons for failure	Adverse events	Microscopy *n/N*, % (95%CI)	Culture *n/N*, % (95%CI)	Sputum induction *n/N*, % (95%CI)	Other methods *n/N*, % (95%CI)	Specificity of sputum induction microscopy vs. culture
Al-Aghbari[46]	Direct ZN	Solid (Ogawa)	82/88, 93.1 (85.7–97.4)	NS	NS	6/82, 7.3 (2.7–15.2)	13/82, 15.9 (8.7–25.6)	6/13, 46.2 (19.2–74.9)	Nasopharyngeal aspirate 10/14, 71.4 (41.9–91.6) Gastric aspirate 10/19, 52.6 (28.9–75.6)	NS
Al Zahrani[50]	Concentrated fluorescent	Liquid (BACTEC™ 460) + solid (LJ)	500/503, 99.4 (98.2–99.9)	NS	NS	10/500, 2 (1.0–3.6)	44/500, 8.8 (6.5–11.6)	10/44, 22.7 (11.5–37.8)	NA	NS
Atiq-ur-Rehman[13]	Direct ZN	Solid (LJ)	132/164, 80.5 (73.6–86.3)	NS	Cough (21; 5 led to bronchospasm) Nausea (19)	28/132, 21.2 (14.6–29.2)	36/132, 27.3 (19.9–35.7)	28/36, 77.8 (60.8–89.9)	NA	NS
Bell[41]	Concentrated ZN	Solid (LJ)	111/111, 100 (96.7–100)	—	NS	4/111, 3.6 (1.0–9.0)	9/111, 8.1 (3.8–14.8)	4/9, 44.4 (13.7–78.8)	Physiotherapy 5/10, 50 (18.7–81.3) Gastric washing 3/10, 30 (6.7–65.2) BAL 3/6, 50 (11.8–88.2)	NS
Breen[53]	Fluorescent, unclear if concentrated	Unclear	42/42, 100 (91.6–100)	—	NS	4/42, 9.5 (2.7–22.6)	13/42, 40.0 (17.6–47.1)	4/13, 30.8 (9.1–61.4)	NA	NS
Brown[14]	Concentrated fluorescent	Liquid (BacT/ALERT®)	107/140, 76.4 (68.5–83.2)	NS (excluded if fewer than 5 samples provided)	Intolerance (1/126)*	13/107, 12.1 (6.6–19.9)	42/107, 39.2 (30.0–49.2)	13/42, 30.9 (17.6–47.1)	Gastric aspirate 12/32, 37.5 (21.1–56.3) BAL 5/21, 23.8 (8.2–47.2)	NS
Iriso[36]	ZN, unclear if concentrated	Solid (LJ)	101/101, 100 (96.4–100)	—	NS	12/101, 11.9 (6.3–19.8)	30/101, 29.7 (21.0–39.6)	12/30, 40 (22.7–59.4)	NA	NS
Kawada[49]	ZN, unclear if concentrated	Solid (Ogawa)	22/22, 100 (84.6–100)	—	NS	5/22, 22.7 (7.8–45.4)	17/22, 77.3 (54.6–92.2)	5/17, 29.4 (10.3–60.0)	Gastric aspirate 1/7, 14.3 (0.4–57.9)	NS
Kawada[47]	ZN, unclear if concentrated	Solid (Ogawa)	25/27, 92.6 (75.7–99.1)	NS	NS	0/25, 0.0 (0–13.7)	12/25, 48 (27.8–68.7)	0/12, 0.0 (0–26.5)	NA	NTM isolated from 4 patients; these were excluded from the study
Klein[51]	Fluorescent, unclear if concentrated	Solid (LJ + Middlebrook 7H10)	519/563, 92.2 (89.7–94.3)‡	Inadequate for staining or smear	NS	6/373, 1.6 (0.1–3.5)	9/373, 2.4 (1.1–4.5%)	6/9, 66.7 (29.9–92.5)§	NA	Microscopy: 2/373 (0.54%) = *M. avium* complex Culture: 64/373 (17.2%) = NTM
Kranzer[45]	Fluorescent, concentrated	Liquid (MGIT)	109/114, 95.6 (90.0–98.6)	NS	None	3/109, 2.7 (0.6–7.8)	7/109, 6.4 (2.6–12.8)	3/7, 42.9 (9.9–81.6)	NA	Speciation performed, no NTM reported
Merrick[16]	Kinyoun, unclear if concentrated	NS	24 (denominator unclear)	NS	NS	6/24, 25 (9.8–46.7)	24/24, 100 (85.8–100)	6/24, 25 (9.8–46.7)	NA	NS

Moore[44]	Fluorescent, concentrated	Liquid (MGIT)	268/270, 99.3 (97.3–99.9)	NS	Nose bleed 75/496, 15.1 (12.1–18.6) Vomiting 11/496, 2 (1.1–3.9) Increased cough 30/496, 6 (4.1–8.5) Wheeze 3/496, 0.6 (0.1–1.8)	17/270, 6.3 (3.7–9.9)	12/270, 4.4 (2.3–7.6)	17/12, 100	NA	All culture-positive samples *M. tuberculosis*
Morse[42]	Fluorescent, concentrated	Solid (LJ)	139/140, 99.3 (96.1–100.0)	Failure to produce sputum	Vomiting 2/140, 1.4 (0.2–5.1)	18/139, 12.9 (7.9–20.0)	48/139, 34.5 (26.7–43.1)	18/48, 37.5 (24.0–52.3)	Microscopy not performed on other methods	NS
Parry[37]	Direct ZN or fluorescent	Solid (LJ)	73/82, 89.0 (80.2–94.9)	NS	0/73	18/73, 24.7 (15.3–36.1)	30/73, 41.1 (29.7–53.2)	18/30, 60 (40.6–77.3)	NA	All culture-positive samples *M. tuberculosis* complex
Saglam[48]	ZN, unclear if concentrated	Solid (LJ)	55/55, 100 (93.5–100)	NA	0/55	23/55, 41.8 (28.7–55.9)	31/55, 56.4 (42.3–69.7)	23/31, 74.2 (55.4–88.1)	BAL 26/33, 78.8 (61.1–91.0)	NS
Schoch[54]	ZN, unclear if concentrated	Solid and liquid - media not stated	91/91, 100 (96.0–100)	NA	NS	8/91, 8.8 (3.9–16.6)	17/91, 18.7 (11.3–28.2)	8/17, 47.1 (23.0–72.2)	BAL 4/15, 26.7 (7.8–55.1)	NS
Shata[38]	ZN, unclear if concentrated	Solid (LJ)	29/30 96.6 (82.8–99.1)	NS	0/30	4/29, 13.8 (3.9–31.6)	7/29, 24.1 (10.3–43.5)	4/7, 57.1 (18.4–90.1)	NA	1 sample microscopy-positive and culture-negative
Souza Pinto[52]	ZN, unclear if concentrated	Solid (LJ)	132/132, 100 (97.2–100)	NA	NS	12/132, 9.1 (4.8–15.3)	18/132, 13.6 (8.2–20.7)	12/18, 66.6 (41.0–86.7)	Physiotherapy 21/18 (116.6)	9/34 (26.5%) of all strains cultured NTM; number occurring in induced sputum samples unclear
Toubes[17]	Fluorescent, unclear if concentrated	Solid (LJ + Middlebrook)	89/94, 94.7 (88.0–98.3)	Nausea	Nausea 1/94	8/89, 9.0 (4.0–16.9)	39/89, 43.8 (33.3–54.7)	8/39, 20.5 (9.3–36.5)	NA	2 samples culture-positive for NTM; unclear if these samples were included in analysis
Wilson[43]	Fluorescent, unclear if concentrated	Liquid (MGIT) and solid (LJ)	136/147, 92.5 (87.0–96.2)	NS	NS	33/130, 25.8 (18.2–33.8)	86/130, 66.2 (57.3–74.2)	33/86, 38.4 (28.0–49.5)	Urine 7/43, 16.3 (6.8–30.7) Blood NA/36 Lymph node biopsy 21/17, 123.5 Pleural/ascetic exudate NA/14 Cold abscess aspirate 5/10, 50 (18.7–81.3)	Speciation performed: no NTM described
Zar[40]	Concentrated fluorescent	Liquid (BACTEC™ 12B)	142/149, 95.3 (90.6–98.1)	Too ill; increasing tachypnoea or cough	Mild epistaxis (6/142) Coughing (8/142) Wheezing (3/142)	13/142, 9.1 (5.0–15.1)	15/142, 10.6 (6.0–16.8)	3/15, 20 (4.3–48.1)	Gastric aspirate 3/9, 33.3 (7.5–70.1)	Not stated
Zar[39]	Concentrated fluorescent	Liquid (BACTEC™ 12B)	250/250, 100 (98.5–100)	NA	Coughing¶ (293/721) Epistaxis (55/721) Vomiting (3/721) Wheezing 2/721	25/250, 10.0 (6.6–14.4)	51/250, 20.4 (15.6–25.9)	25/51, 49.0 (34.8–63.4)	Gastric aspirate 17/38, 44.7 (28.6–61.7)	Sputum samples from 4 children (6%) microscopy-positive, culture-negative

*Denominator includes patients who underwent at least one induction.
†2/22 could only expectorate when saline concentration was increased from 3% to 5%.
‡Study reports number of adequate sputum samples collected rather than number of patients.
§Excludes NTM.
¶Data refer to number of inductions.
ZN = Ziehl-Neelsen; NS = not stated; LJ = Löwenstein-Jensen; NA = not applicable; BAL = bronchioalveolar lavage; NTM = non-tuberculosis mycobacteria; MGIT = Mycobacteria Growth Indicator Tube.

RÉSUMÉ

CONTEXTE : Dans les contextes à ressources limitées, on utilise l'examen microscopique des crachats pour le diagnostic de la tuberculose (TB), mais la sensibilité de ce test est médiocre et les taux de détection des cas sont faibles. On a proposé l'expectoration provoquée comme moyen d'améliorer le recueil des échantillons et de renforcer la sensibilité du test.

OBJECTIF : Entreprendre une revue systématique des études comparant la sensibilité de la bacilloscopie et de la culture dans les échantillons d'expectorations provoquées.

MÉTHODES : Nous avons mené en double des recherches des bases de données jusqu'à août 2011 et des sites accessibles concernant les principales conférences sur le VIH et la TB (jusqu'à novembre 2010) afin d'identifier les études comparant les performances de la bacilloscopie par comparaison avec la culture dans les échantillons d'expectorations provoquées en utilisant comme standard de référence le résultat de la culture.

RÉSULTATS : Nos critères d'inclusion ont été rencontrés dans 23 études. Les taux globaux de succès de l'induction ont été élevés, allant de 76,4% (IC95% 68,5–83,2) à 100% (IC95% 98,5–100), alors que les effets indésirables associés à l'induction des expectorations étaient rares et peu graves. La sensibilité de l'examen microscopique par comparaison avec la culture s'est étalée entre 0% et 100% ; huit études seulement ont signalé l'espèce de mycobactéries isolée par la culture. Le rendement est généralement plus élevé pour l'induction des crachats par comparaison avec l'aspiration naso-pharyngienne et le tubage gastrique et se compare à égalité avec le lavage broncho-alvéolaire et la physiothérapie.

DISCUSSION : L'induction des crachats augmente le taux de détection des cas de TB et est utile chez les sujets dont l'examen direct des frottis d'expectoration spontanée est négatif ou qui sont incapables d'expectorer spontanément. Cette technique est bien tolérée chez les enfants et les adultes, quel que soit leur statut VIH, et peut être utilisée lorsque la culture n'est pas disponible. L'utilisation d'échantillons de crachats provoqués pour les tests moléculaires tels que Xpert® MTB/RIF mérite des investigations complémentaires.

RESUMEN

MARCO DE REFERENCIA: En los entornos con recursos limitados el diagnóstico de la tuberculosis (TB) se basa en el examen microscópico del esputo, pero la sensibilidad de esta prueba es baja y se logran tasas bajas de detección de casos.

OBJETIVO: Utilizar la inducción del esputo como un método que permite mejorar la calidad de las muestras recogidas y aumentar la sensibilidad de la prueba. Se llevó a cabo un análisis sistemático de los estudios publicados que comparan la sensibilidad de la baciloscopia y el cultivo en las muestras obtenidas mediante inducción del esputo.

MÉTODOS: Se llevaron a cabo búsquedas sistemáticas en duplicado en las bases de datos (hasta agosto del 2011) y en los sitios web consultables de las principales conferencias sobre la infección por el virus de la inmunodeficiencia humana (VIH) y la TB (hasta noviembre del 2010), con el fin de escoger los estudios que comparaban el rendimiento diagnóstico de la baciloscopia y el cultivo en muestras de esputo inducido, tomando el cultivo como norma de referencia.

RESULTADOS: Veintitrés estudios cumplieron con los criterios de inclusión. La eficacia global de la inducción fue alta, entre 76,4% (95%IC 68,5–83,2) y 100% (IC95% 98,5–100) y los efectos adversos relacionados con la inducción del esputo fueron infrecuentes y leves. La sensibilidad del examen microscópico comparado con el cultivo osciló entre 0% y 100%; solo en ocho estudios se comunicó la especie de micobacteria aislada en el cultivo. El rendimiento diagnóstico fue generalmente superior con las muestras obtenidas mediante la inducción del esputo que con la aspiración nasofaríngea o el lavado gástrico y fue equivalente al rendimiento de las muestras tomadas durante el lavado broncoalveolar o con la asistencia de la fisioterapia.

CONCLUSIÓN: La inducción del esputo aumenta la detección de casos de TB y es útil en las personas con una baciloscopia negativa en muestras recogidas de manera natural o en quienes no consiguen expectorar espontáneamente. La inducción es bien tolerada por los niños y los adultos, independientemente de su estado frente al VIH y se puede realizar en medios donde no se cuenta con el cultivo. Se debe ampliar la investigación con las muestras de esputo inducido al uso de las pruebas moleculares como el Xpert® MTB/RIF.