1 Appendices: Evidence Tables – Diagnosis of active TB RQ B

Contents

1.1 RQB: What is the most effective method of collecting respiratory samples from children unable to expectorate spontaneously?

1.1.1 Abadco and Steiner, 1992

Bibliographic reference	**Abadco DL and Steiner P (1992) Gastric lavage is better than bronchoalveolar lavage for isolation of Mycobacterium tuberculosis in childhood pulmonary tuberculosis. *Pediatric Infectious Disease Journal* 11(9): 735-8**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes*

Bibliographic reference	**Abadco DL and Steiner P (1992) Gastric lavage is better than bronchoalveolar lavage for isolation of Mycobacterium tuberculosis in childhood pulmonary tuberculosis. *Pediatric Infectious Disease Journal* 11(9): 735-8**
	Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 20
Patient characteristics	*Inclusion* Admitted to the Children's Medical Centre of Brooklyn for gastric lavage and bronchoalveolar lavage *Characteristics of included participants* 19 children were diagnosed with pulmonary tuberculosis based on a positive tuberculin skin test (induration ≥10 mm) and an abnormal chest roentogram 1 patient with AIDS had an abnormal chest roentogram but a negative tuberculin skin test, but was included in the study because of a history of exposure to active tuberculosis 10 males, 10 females Ages ranged from 4 months to 7.5 years (median = 24 months) 16 participants were <5 years of age, 4 participants were >5 years of age 4 participants were asymptomatic, 16 had cough and/or fever
Intervention	*Nasogastric lavage* 3 specimens collected on 3 consecutive mornings after an overnight fast Depending on the age of the participant, the child was either allowed to drink 30 to 60 ml of sterile water or it was administered through a nasogastric tube The gastric contents were aspirated through a nasogastric tube and immediately sent for fluorescence microscopy and culture on Löwenstein-Jensen and Middlebrook 7H11 media
Comparator	*Bronchoalveolar lavage* Single specimen collected on the same day as the gastric lavage Patients received meperidine (2 mg/kg), promethazine (1 mg/kg) and chlorpromazine (1 mg/kg) intramuscularly 30 to 60 minutes before the procedure All patients received supplemental oxygen

Bibliographic reference	**Abadco DL and Steiner P (1992) Gastric lavage is better than bronchoalveolar lavage for isolation of Mycobacterium tuberculosis in childhood pulmonary tuberculosis. *Pediatric Infectious Disease Journal* 11(9): 735-8**
	Topical 2% lidocaine was applied to the nose and larynx as needed The flexible bronchoscope was inserted transnasally, advanced into the trachea and wedged into the most involved area as seen on the chest roentogram or into a subsegment of the right middle lobe if the infiltrate was diffuse After wedging, 5 to 10 ml of sterile nonbacteriostatic 0.9% sodium chloride solution was instilled through the suction channel and subsequently aspirated The specimen was immediately sent for fluorescence microscopy and culture on Löwenstein-Jensen and Middlebrook 7H11 media
Location	New York, US
Outcomes measures and effect size	Smear positivity (number positive participants; note: all participants were considered to have tuberculosis) • nasogastric lavage = 0/20 • bronchoalveolar lavage = 0/20 • nasogastric lavage plus bronchoalveolar lavage = 0/20
	Volume of single specimen (mean (range), ml) • nasogastric lavage = 35 (20–55) • bronchoalveolar lavage = 56.5 (45 to 80)
	Need for topical anaesthesia • nasogastric lavage = none documented • bronchoalveolar lavage = 2 participants, each requiring no more than 60 mg
Source of funding	No details provided
Comments	Same population as Chan (1994); duplicate outcomes (culture positivity) extracted from Chan (2004)

1.1.2 Al-Aghbari, 2009

Bibliographic reference	**Al-Aghbari N, Al-Sonboli N, Yassin MA, Coulter JB, Atef Z, Al-Eryani A and Cuevas LE (2009) Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. *PLoS One* 4(4): e5140**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear*

Bibliographic reference	**Al-Aghbari N, Al-Sonboli N, Yassin MA, Coulter JB, Atef Z, Al-Eryani A and Cuevas LE (2009) Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. *PLoS One* 4(4): e5140**
	Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *no, not all collection techniques applied to all participants* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *microscopists blinded; other investigators unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups comparable at baseline? *unclear* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *unclear* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*

Bibliographic reference	**Al-Aghbari N, Al-Sonboli N, Yassin MA, Coulter JB, Atef Z, Al-Eryani A and Cuevas LE (2009) Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. *PLoS One* 4(4): e5140**
Number of patients	Included = 213 participants • nasopharyngeal aspirate = 197 participants • gastric aspirate = 196 participants • induced sputum = 88 participants
Patient characteristics	*Inclusion* Children with suspected tuberculosis, as defined using the following criteria: • a history of contact with cases of pulmonary tuberculosis • children not regaining normal health after measles or whooping cough • unexplained weight loss • the presence of cough and wheeze not responding to antibiotic therapy • X-ray findings suggestive of pulmonary tuberculosis *Characteristics of included participants* Age ranged from 2 months to 15 years, with a median of 5 years and 42 (20%) were <2 years old The most frequent clinical symptoms at presentation were cough (195, 92%), unexplained fever (179, 84%), anorexia (142, 67%), weight loss (125, 59%) and difficult breathing (82, 38%)
Intervention	*Nasopharyngeal aspirate* 1 specimen collected by direct aspiration via a mucus trap connected to a suction device on the first day, without induction of cough or instillation of saline solutions After the preparation of direct smears, specimens were stained using the hot Ziehl Neelsen method; all smears were read and graded by trained microscopists who were unaware of the grading of the previous specimens All specimens were cultured using Ogawa culture media
	Nasogastric aspiration 3 specimens collected Specimens were obtained at 6:00 am on three consecutive days by introducing a nasogastric tube and aspiration of the gastric content with a syringe After the preparation of direct smears, specimens were stained using the hot Ziehl Neelsen method; all smears were read and graded by trained microscopists who were unaware of the grading of the previous specimens All specimens were cultured using Ogawa culture media
Comparator	*Induced sputum* 3 specimens collected using inhaled salbutamol via a metered dose inhaler attached to oxygen at a flow rate of 5 liters per

Bibliographic reference	**Al-Aghbari N, Al-Sonboli N, Yassin MA, Coulter JB, Atef Z, Al-Eryani A and Cuevas LE (2009) Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. *PLoS One* 4(4): e5140**
	minute on 5 ml of 5% sterile saline for 15 minutes, followed by physiotherapy (chest percussion, vibration and active cycle breathing) and sputum collection by expectoration or from the naso/orophrarynx using a mucus extractor in those unable to expectorate After the preparation of direct smears, specimens were stained using the hot Ziehl Neelsen method; all smears were read and graded by trained microscopists who were unaware of the grading of the previous specimens All specimens were cultured using Ogawa culture media
Location	Sana'a, Yemen
Outcomes measures and effect size	Culture positivity (number positive/total number of specimens) • nasopharyngeal aspirate = 14/200 • nasogastric aspirate = 49/564 • induced sputum = 31/216
	Smear positivity (number positive/total number of specimens) • nasopharyngeal aspirate = 10/200 • nasogastric aspirate = 17/564 • induced sputum = 9/216
Source of funding	Dr Al-Aghbari received a study scholarship from the Special Programme for Research in Tropical Diseases of the World Health Organization The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Comments	

1.1.3 Bhandari, 1971

Bibliographic reference	**Bhandari B, Singh SV and Sharma VK (1971) Bacteriological diagnosis of pulmonary tuberculosis. A comparative study of gastric wash, laryngeal swab and lung puncture. *Indian Journal of Pediatrics* 38(284): 349-53**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear*

Bibliographic reference	**Bhandari B, Singh SV and Sharma VK (1971) Bacteriological diagnosis of pulmonary tuberculosis. A comparative study of gastric wash, laryngeal swab and lung puncture. *Indian Journal of Pediatrics* 38(284): 349-53**
	Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 30

Bibliographic reference	**Bhandari B, Singh SV and Sharma VK (1971) Bacteriological diagnosis of pulmonary tuberculosis. A comparative study of gastric wash, laryngeal swab and lung puncture. *Indian Journal of Pediatrics* 38(284): 349-53**
Patient characteristics	*Inclusion* Children with suspected pulmonary tuberculosis who had not received previous antituberculosis treatment *Characteristics of included participants* Age range: 4 months to 13 years ≤5 years = 17 12 females Positive tuberculin skin test (n = 19) = 9 Erythrocyte sedimentation rate (mean±SD (range), mm at 1st hour) = 32±19 (5–61)
Intervention	*Laryngeal swab* 3 specimens collected on 3 consecutive days A sterilised cotton swab was moistened with distilled water and the swab collected with the aid of a laryngoscope Specimens were examined by Gram and Ziehl-Neelsen microscopy, and cultured on Löwenstein-Jensen medium for 6 to 10 weeks
	Lung puncture aspiration 1 specimen collected from every patient The site of the pulmonary lesion was identified clinically and radiologically Skin preparation was achieved with 2% iodine, applied for 2 minutes, and removed with 95% ethanol The thorax was entered with a 4 cm needle and continuous suction applied with a 10 ml syringe Specimens were examined by Gram and Ziehl-Neelsen microscopy, and cultured on Löwenstein-Jensen medium for 6 to 10 weeks

Bibliographic reference	**Bhandari B, Singh SV and Sharma VK (1971) Bacteriological diagnosis of pulmonary tuberculosis. A comparative study of gastric wash, laryngeal swab and lung puncture. *Indian Journal of Pediatrics* 38(284): 349-53**
Comparator	*Gastric lavage* 3 specimens collected early in the morning on 3 consecutive days after an overnight fast A stomach tube was passed and the contents aspirated 30 to 50 ml of distilled water was pushed through the tube and the stomach was, again, aspirated Specimens were examined by Gram and Ziehl-Neelsen microscopy, and cultured on Löwenstein-Jensen medium for 6 to 10 weeks
Location	Udaipur, India
Outcomes measures and effect size	Culture positivity (number of participants with a positive result) • laryngeal swab (3 specimens) = 4/30 • lung puncture aspiration (1 specimen) = 16/30 • gastric lavage (3 specimens) = 3/30 *≤5 years* • laryngeal swab (3 specimens) = 3/17 • lung puncture aspiration (1 specimen) = 10/17 • gastric lavage (3 specimens) = 3/17 *>5 years* • laryngeal swab (3 specimens) = 1/13 • lung puncture aspiration (1 specimen) = 6/13 • gastric lavage (3 specimens) = 0/13

Bibliographic reference	**Bhandari B, Singh SV and Sharma VK (1971) Bacteriological diagnosis of pulmonary tuberculosis. A comparative study of gastric wash, laryngeal swab and lung puncture. *Indian Journal of Pediatrics* 38(284): 349-53**
	Smear positivity (number of participants with a positive result) • laryngeal swab (3 specimens) = 6/30 • lung puncture aspiration (1 specimen) = 5/30 • gastric lavage (3 specimens) = 4/30 *≤5 years* • laryngeal swab (3 specimens) = 4/17 • lung puncture aspiration (1 specimen) = 4/17 • gastric lavage (3 specimens) = 3/17 *>5 years* • laryngeal swab (3 specimens) = 2/13 • lung puncture aspiration (1 specimen) = 1/13 • gastric lavage (3 specimens) = 1/13
Source of funding	No details provided
Comments	
Abbreviations: SD, standard deviation	

1.1.4 Buonsenso, 2014

Bibliographic reference	**Buonsenso D, Barone G, Valentini P, Pierri F, Riccardi R and Chiaretti A (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double-blind, placebo controlled, randomized study. *BMC Pediatrics* 14: 67**

Bibliographic reference	**Buonsenso D, Barone G, Valentini P, Pierri F, Riccardi R and Chiaretti A (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double-blind, placebo controlled, randomized study. *BMC Pediatrics* 14: 67**
Study type	Randomised controlled trial
Study quality	*Study limitations* Appropriate method of randomisation? *yes* Adequate allocation concealment? *yes* Participants blinded? *unclear* Individuals administering care blinded? *yes* Investigators blinded to intervention? *yes* Investigators blinded to confounding and prognostic factors? *yes* Appropriate length of follow-up? *yes* Precise definition of outcome? *yes* Valid and reliable method of outcome measurement? *yes* Intent-to-treat principle adhered to? *yes* *Inconsistency* Groups comparable at baseline? *yes, although information provided relates only to age and disease status* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups equivalent for intervention completion? *yes* Groups comparable for availability of data? *yes* *Indirectness*

Bibliographic reference	**Buonsenso D, Barone G, Valentini P, Pierri F, Riccardi R and Chiaretti A (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double-blind, placebo controlled, randomized study. *BMC Pediatrics* 14: 67**
	Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Randomised/analysed = 36 • nasogastric aspiration with sedation = 19 • nasogastric aspiration with placebo = 17 Number of procedures performed = 108 • nasogastric aspiration with sedation = 57 • nasogastric aspiration with placebo = 51
Patient characteristics	*Inclusion* Children <14 years old 'Uncooperative'[a] children undergoing gastric aspirates for suspected tuberculosis *Exclusion* ASA physical status classification of III (patient with severe systemic disease) or higher Known allergy to benzodiazepines Known allergy to ketamine Upper respiratory tract infection with nasal discharge Known liver disease or respiratory distress *Characteristics of included participants* Age (mean±SD, months) • nasogastric aspiration with sedation = 41.5±36.0 • nasogastric aspiration with placebo = 40.6±34.8 Final diagnosis • nasogastric aspiration with sedation: pulmonary tuberculosis = 15; latent tuberculosis = 1; non-tuberculous pneumonia = 3 • nasogastric aspiration with placebo: pulmonary tuberculosis = 17 The two groups did not differ significantly with respect to weight and ethnicity
Intervention	*Nasogastric aspiration with intranasal sedation* Intranasal sedation using 2 mg/kg of ketamine hydrochloride in both nostrils, followed by 0.5 mg/kg (maximum dose 10 mg) of midazolam using a mucosal atomizer device

Bibliographic reference	**Buonsenso D, Barone G, Valentini P, Pierri F, Riccardi R and Chiaretti A (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double-blind, placebo controlled, randomized study. *BMC Pediatrics* 14: 67**
	Gastric washings were performed on three consecutive days early in the morning and after an overnight fasting A nasogastric tube was inserted into the child's stomach after intranasal administration (without any additional drugs nor topical anaesthetics on nasogastic tube) and then aspirated its contents; in case of unsuccessful or poor aspiration, the volume of gastric aspirates was augmented as needed by injecting in the stomach 5 mL of saline solution (sterile water) and aspirating back The procedure began in every case within 60 minutes from intranasal administration
Comparator	*Nasogastric aspiration with placebo* Intranasal administration of normal saline solution (the same volume the child would have received if in the sedation-group) in each nostril (twice, in order to pretend the two different drugs of the sedation-group) using a mucosal atomizer device Gastric washings were performed on three consecutive days early in the morning and after an overnight fasting A nasogastric tube was inserted into the child's stomach after intranasal administration (without any additional drugs nor topical anaesthetics on nasogastic tube) and then aspirated its contents; in case of unsuccessful or poor aspiration, the volume of gastric aspirates was augmented as needed by injecting in the stomach 5 mL of saline solution (sterile water) and aspirating back The procedure began in every case within 60 minutes from intranasal administration
Location	Rome, Italy
Outcomes measures and effect size	Acceptability of the procedure to parents[c] *Median score (range) provided by parents of those receiving sedation (n = 19)* / *Median score (range) provided by parents of those receiving placebo (n = 19)* Did the sedation help? 10 (10–10) / 5 (3–7) Level of child's outlook 8.9 (7–10) / 5.8 (5–7) Level of parents' outlook 9.1 (8–10) / 4.9 (3–7) Level of child's tolerance of procedures 8.7 (7–10) / 8.5 (7–10) Would recommend to other parents 9.3 (9–10) / 4 (3–6) Would like to see the mucosal atomizer device used routinely 9.8 (9–10) / 4 (3–6)
	Acceptability of the procedure to clinicians[c] *Median score (range) provided by parents of those receiving sedation* / *Median score (range) provided by parents of those receiving placebo*

Bibliographic reference	**Buonsenso D, Barone G, Valentini P, Pierri F, Riccardi R and Chiaretti A (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double-blind, placebo controlled, randomized study. *BMC Pediatrics* 14: 67**		
	Did the sedation help?	10 (10–10)	3 (2–4)
	Level of child's outlook	8 (7–9)	3 (2–4)
	Level of clinicians' outlook	9.5 (9–10)	4 (3–5)
	Level of child's tolerance of procedures	8.2 (7–9)	8 (7–9)
	Would recommend to other clinicians	9.4 (9–10)	3 (1–5)
	Would like to see the mucosal atomizer device used routinely	10 (10–10)	3 (1–5)
	Made the procedure more acceptable	10 (10–10)	3 (1–5)
	Adverse events - transitory postsedation agitation Number of procedures after which transitory postsedation agitation was experienced • nasogastric aspiration with sedation (n = 57 procedures) = 6 • nasogastric aspiration with placebo (n = 51 procedures) = 0		
Source of funding	No funding have been received by the authors		
Comments			
[a] Pre-sedation behaviour was assessed on a 4-point scale (1 = calm, cooperative; 2 = anxious but reassurable; 3 = anxious and not reassurable; 4 = crying or resisting) by an anesthesiologist blinded to the group of the child; children were included if they were <14 years old and had a pre-sedation behaviour ≥3 [b] Modified Objective Pain Score; score ranges from 0 to 10 (the higher the score, the greater the pain experienced for the child) [c] Derived from a series of questions, answered using a visual analogue scale ('0' for worst, '10' for best) Abbreviations: SD, standard deviation		

1.1.5 Cakir, 2008

Bibliographic reference	**Cakir E, Uyan ZS, Oktem S, Karakoc F, Ersu R, Karadag B and Dagli E (2008) Flexible bronchoscopy for diagnosis and follow up of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 27(9): 783-7**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear*

Bibliographic reference	**Cakir E, Uyan ZS, Oktem S, Karakoc F, Ersu R, Karadag B and Dagli E (2008) Flexible bronchoscopy for diagnosis and follow up of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 27(9): 783-7**
	Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes, although details provided were limited* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups comparable at baseline? *unclear* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 70
Patient characteristics	*Inclusion* Children

Bibliographic reference	**Cakir E, Uyan ZS, Oktem S, Karakoc F, Ersu R, Karadag B and Dagli E (2008) Flexible bronchoscopy for diagnosis and follow up of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 27(9): 783-7**
	Tuberculosis patients with an inadequate response to antituberculosis treatment, defined as unresolved or progressive clinical and radiographic findings despite 8 weeks of antituberculosis treatment Patients with suspected tuberculosis, defined as children with respiratory symptoms and chest radiograph findings suspicious of tuberculosis, with or without positive tuberculin skin test and history of a household contact with tuberculosis *Characteristics of included participants* Age (median [interquartile range], months) = 81.5 [13.7–112.5] Gender • male = 38 • female = 32 Symptoms • cough = 62 • sputum = 24 • fever = 13 • dyspnea = 11 Duration of symptoms (mean±SD) = 3.54±3.05 Household contact with active tuberculosis = 31 Positive tuberculin skin test = 38 High erythrocyte sedimentation rate = 34 Tracheobronchial involvement = 33 *Mycobacterium tuberculosis* isolation = 14
Intervention	*Nasogastric aspiration* All cases were hospitalized Specimens collected on 3 consecutive days All samples were cultured in Löwenstein-Jensen medium
Comparator	*Bronchoalveolar lavage* All cases were hospitalized Patients received midazolam and pethidine HCL as premedication and lidocaine was used as topical anesthetic All samples were cultured in Löwenstein-Jensen medium
Location	Istanbul, Turkey
Outcomes measures and effect size	Culture positivity (number positive/total number of participants) • nasogastric aspiration = 5/70

Bibliographic reference	**Cakir E, Uyan ZS, Oktem S, Karakoc F, Ersu R, Karadag B and Dagli E (2008) Flexible bronchoscopy for diagnosis and follow up of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 27(9): 783-7**
	• bronchoalveolar lavage = 7/70
Source of funding	No details provided
Comments	
Abbreviations: SD, standard deviation	

1.1.6 Cakir, 2013

Bibliographic reference	**Cakir E, Kut A, Ozkaya E, Gedik AH, Midyat L and Nursoy M (2013) Bronchoscopic evaluation in childhood pulmonary tuberculosis: risk factors of airway involvement and contribution to the bacteriologic diagnosis. *Pediatric Infectious Disease Journal* 32(8): 921-3**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *unclear* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency*

Bibliographic reference	**Cakir E, Kut A, Ozkaya E, Gedik AH, Midyat L and Nursoy M (2013) Bronchoscopic evaluation in childhood pulmonary tuberculosis: risk factors of airway involvement and contribution to the bacteriologic diagnosis. *Pediatric Infectious Disease Journal* 32(8): 921-3**
	Groups comparable at baseline? *yes* Groups received the same care apart from the intervention(s) studied? *yes, although details provided were limited* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 167 participants
Patient characteristics	*Inclusion* Children with suspected tuberculosis, in accordance with the World Health Organization's TB Standards case definition *Characteristics of included participants* Age (mean±SD (range), months) = 97.2±48.5 (2 months to 16 years) Male = 54% Contact with a known adult index case = 78% Positive tuberculin skin test = 67% Primary tuberculosis = 82% Signs and symptoms • cough = 76% • fever = 26% • weight loss = 20% • haemoptysis = 12% • wheezing = 5%

Bibliographic reference	**Cakir E, Kut A, Ozkaya E, Gedik AH, Midyat L and Nursoy M (2013) Bronchoscopic evaluation in childhood pulmonary tuberculosis: risk factors of airway involvement and contribution to the bacteriologic diagnosis. *Pediatric Infectious Disease Journal* 32(8): 921-3**
	• pulmonary consolidation = 61% • atelectasis = 19% • cavity = 11% • disseminated infiltration = 7% There was no statistical difference between these 2 groups for demographic features, symptoms and radiologic findings
Intervention	*Nasogastric aspiration* Early morning specimens collected on 3 consecutive days All samples were cultured in Löwenstein-Jensen medium
Comparator	*Bronchoalveolar lavage* All samples were cultured in Löwenstein-Jensen medium
Location	Istanbul, Turkey
Outcomes measures and effect size	Culture positivity (number positive/total number of patients (%)) • nasogastric aspiration = 54/167 • bronchoalveolar lavage = 48/167 • nasogastric aspiration plus bronchoalveolar lavage = 70/167
Source of funding	No details provided
Comments	
Abbreviations: SD, standard deviation	

1.1.7 Chan, 1994

Bibliographic reference	**Chan S, Abadco DL and Steiner P (1994) Role of flexible fiberoptic bronchoscopy in the diagnosis of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 13(6): 506-9**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *yes* Was a case-control design avoided? *yes*

Bibliographic reference	**Chan S, Abadco DL and Steiner P (1994) Role of flexible fiberoptic bronchoscopy in the diagnosis of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 13(6): 506-9**
	Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	n = 36
Patient characteristics	*Inclusion* Children under 16 years of age admitted to the Children's Medical Centre of Brooklyn for gastric lavage and bronchoalveolar lavage

Bibliographic reference	**Chan S, Abadco DL and Steiner P (1994) Role of flexible fiberoptic bronchoscopy in the diagnosis of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 13(6): 506-9**
	Characteristics of included participants 19 males, 17 females Age (median (range)) = 3.9 years (4 months – 16 years) Symptoms on presentation included fever (n = 20), cough (n = 16) and wheezing (n = 2); 12 patients were asymptomatic A history of close contact with tuberculosis in an adult with active tuberculosis was elicited in 12 patients
Intervention	*Nasogastric lavage* 3 specimens collected on 3 consecutive mornings after an overnight fast Depending on the age of the participant, the child was either allowed to drink 30 to 60 ml of sterile water or it was administered through a nasogastric tube The gastric contents were aspirated through a nasogastric tube and immediately sent for fluorescence microscopy and culture on Löwenstein-Jensen and Middlebrook 7H11 media
Comparator	*Bronchoalveolar lavage* Single specimen collected on the same day as the gastric lavage Patients received meperidine (2 mg/kg), promethazine (1 mg/kg) and chlorpromazine (1 mg/kg) intramuscularly 30 to 60 minutes before the procedure All patients received supplemental oxygen Topical 2% lidocaine was applied to the nose and larynx as needed The flexible bronchoscope was inserted transnasally, advanced into the trachea and wedged into the most involved area as seen on the chest roentogram or into a subsegment of the right middle lobe if the infiltrate was diffuse After wedging, 5 to 10 ml of sterile nonbacteriostatic 0.9% sodium chloride solution was instilled through the suction channel and subsequently aspirated The specimen was immediately sent for fluorescence microscopy and culture on Löwenstein-Jensen and Middlebrook 7H11 media
Location	New York, US
Outcomes measures and effect size	Culture positivity (number positive participants; note: all participants were considered to have tuberculosis) • nasogastric lavage = 17/36 • bronchoalveolar lavage = 4/36
Source of funding	No details provided

Bibliographic reference	**Chan S, Abadco DL and Steiner P (1994) Role of flexible fiberoptic bronchoscopy in the diagnosis of childhood endobronchial tuberculosis. *Pediatric Infectious Disease Journal* 13(6): 506-9**
Comments	

1.1.8 Hatherill, 2009

Bibliographic reference	**Hatherill M, Hawkridge T, Zar HJ, Whitelaw A, Tameris M, Workman L, Geiter L, Hanekom WA and Hussey G (2009) Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? *Archives of Disease in Childhood* 94(3): 195-201**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes, though details provided were limited* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups comparable at baseline? *unclear* Groups received the same care apart from the intervention(s) studied? *yes*

Bibliographic reference	**Hatherill M, Hawkridge T, Zar HJ, Whitelaw A, Tameris M, Workman L, Geiter L, Hanekom WA and Hussey G (2009) Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? *Archives of Disease in Childhood* 94(3): 195-201**
	Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 1936 specimens
Patient characteristics	*Inclusion* Children with a tuberculosis contact or compatible symptoms – such as unexplained cough, loss of weight, or failure to thrive – being investigated for suspected pulmonary tuberculosis *Characteristics of included participants* Age (median [interquartile range], months) = 13 [7–20] History of household tuberculosis exposure = 892 (48%) Signs and symptoms: • failure to thrive = 1045 (56%) • weight loss = 415 (22%) • history of cough of any duration = 1064 (57%), including 743 (40%) with cough for >2 weeks • history of fever = 715 cases (38%) • chest radiographs judged compatible with a diagnosis of pulmonary tuberculosis = 369 (20%) • positive tuberculin skin test = 676 (36%) Positive HIV ELISA = 60 (3.2%), of which 32 (1.7%) were confirmed HIV-infected by PCR
Intervention	*Nasogastric lavage* Early morning specimens collected on 2 consecutive days after overnight fast Uses 10 ml 0.9% saline and aspiration of 5–10 ml lavage fluid via a nasogastric tube; sputum induction was performed 3–4 hours later Culture was performed using the BACTEC MGIT 960

<table>
<tr><th>Bibliographic reference</th><th>Hatherill M, Hawkridge T, Zar HJ, Whitelaw A, Tameris M, Workman L, Geiter L, Hanekom WA and Hussey G (2009) Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? Archives of Disease in Childhood 94(3): 195-201</th></tr>
<tr><td>Comparator</td><td>Induced sputum
Specimens collected on 2 consecutive days
Sputum induction was performed by an experienced research nurse under continuous monitoring of pulse and oxygen saturation, preceded by administration of 200 µg salbutamol through a metered dose inhaler and spacer; hypertonic 5% saline (5 ml) was delivered by jet nebulisation at an oxygen flow of 5 litres/min, and the sample was collected by suctioning of the oropharynx
Culture was performed using the BACTEC MGIT 960</td></tr>
<tr><td>Location</td><td>South Africa</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Culture positivity (number positive/total number of cases (%))
• nasogastric lavage = 127/1869
• induced sputum = 108/1869
K statistic = 0.31
Comparative and cumulative yields (number cases positive by each collection method/total number of culture positive cases)
<table>
<tr><th></th><th>Culture positive</th><th>Yield (%) (95% CI)</th></tr>
<tr><td>Induced sputum</td><td></td><td></td></tr>
<tr><td>day 1</td><td>73</td><td>38 (31 to 45)</td></tr>
<tr><td>day 2</td><td>51</td><td>27 (20 to 33)</td></tr>
<tr><td>days 1 and 2</td><td>106</td><td>55 (48 to 62)</td></tr>
<tr><td>Gastric lavage</td><td></td><td></td></tr>
<tr><td>day 1</td><td>80</td><td>42 (35 to 49)</td></tr>
<tr><td>day 2</td><td>75</td><td>39 (32 to 46)</td></tr>
<tr><td>days 1 and 2</td><td>125</td><td>66 (59 to 73)</td></tr>
</table>
Differences in yield between various comparisons of single, cumulative and combined yields among case episodes with a positive M. tuberculosis culture (n=191)
<table>
<tr><th>Sample type</th><th>Number culture positive</th><th>Yield (%)</th><th>Sample type</th><th>Number culture positive</th><th>Yield (%)</th><th>Difference in yield (%) (95% CI)</th></tr>
<tr><td>Single induced sputum (day 1)</td><td>73</td><td>38</td><td>Single gastric lavage (day 1)</td><td>80</td><td>42</td><td>-4 (-15 to 7)</td></tr>
<tr><td>Single induced</td><td>73</td><td>38</td><td>Cumulative induced</td><td>106</td><td>55</td><td>-17 (-23 to -11)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Hatherill M, Hawkridge T, Zar HJ, Whitelaw A, Tameris M, Workman L, Geiter L, Hanekom WA and Hussey G (2009) Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? *Archives of Disease in Childhood* 94(3): 195-201						
	sputum (day 1)			sputum (days 1 + 2)			
	Single induced sputum (day 1)	73	38	Cumulative gastric lavage (days 1 + 2)	126	66	-28 (-40 to -15)
	Single gastric lavage (day 1)	80	42	Cumulative gastric lavage (days 1 + 2)	126	66	-24 (-31 to -17)
	Single gastric lavage (day 1)	80	42	Cumulative induced sputum (days 1 + 2)	106	55	-13 (-25 to -2)
	Cumulative gastric lavage (days 1 + 2)	126	66	Cumulative induced sputum (days 1 + 2)	106	55	11 (-3 to 24)
	Cumulative gastric lavage (days 1 + 2)	126	66	Combined induced sputum and gastric lavage (day 1)	128	67	-1 (-11 to 9)
	Cumulative induced sputum (days 1 + 2)	106	55	Combined induced sputum and gastric lavage (day 1)	128	67	-12 (-21 to -2)
Source of funding	Supported by the Aeras Global TB Vaccine Foundation, EuropeAID; the National Institutes for Health, Immunopaedia, the Dana Foundation, the Bill and Melinda Gates Foundation and the European and Developing Countries Trials Partnership						
Comments							
Abbreviations: CI, confidence interval							

1.1.9 Jiménez, 2013

Bibliographic reference	Jiménez MR, Guillén Martín S, Prieto Tato LM, Cacho Calvo JB, Alvarez García A, Soto Sánchez B and Ramos Amador JT (2013) Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infectious Diseases* 13(1): 222
Study type	Cross-sectional
Study quality	*Study limitations*

Bibliographic reference	**Jiménez MR, Guillén Martín S, Prieto Tato LM, Cacho Calvo JB, Alvarez García A, Soto Sánchez B and Ramos Amador JT (2013) Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infectious Diseases* 13(1): 222**
	Was a consecutive or random sample of patients enrolled? *yes* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *no, excluded participants positive for non-tuberculous mycobacteria* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes*

Bibliographic reference	**Jiménez MR, Guillén Martín S, Prieto Tato LM, Cacho Calvo JB, Alvarez García A, Soto Sánchez B and Ramos Amador JT (2013) Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infectious Diseases* 13(1): 222**
	Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 22 participants 1 participant was excluded for not having provided the collection of samples according to the protocol 4 patients were excluded because the final diagnosis was not PTB and other microorganisms were identified Data available = 17 participants
Patient characteristics	*Inclusion* Children (<15 years old) with suspected pulmonary tuberculosis based on clinical features or radiology No evidence of immunosuppression *Characteristics of included participants* 11 patients (53%) were females Median age was 72 months (range 1 month to 14 years of age) 7 (33%) were ≤5 years of age 17 patients (80%) were clinically diagnosed of pulmonary tuberculosis, based on a positive tuberculin skin test (Mantoux reaction was >10 mm) and radiological criteria An HIV-test (enzyme-linked immunoassay) was performed on only one patient, with negative results
Intervention	*Gastric lavage* 3 specimens collected on consecutive days Performed early morning on all children, after an overnight fast A nasogastric tube was passed and normal saline 20 ml inserted, left for 3 minutes and then aspirated

Bibliographic reference	**Jiménez MR, Guillén Martín S, Prieto Tato LM, Cacho Calvo JB, Alvarez García A, Soto Sánchez B and Ramos Amador JT (2013) Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infectious Diseases* 13(1): 222**
	An additional 5–10 ml of normal saline was introduced and aspirated, until a minimum of 20 ml of aspirate was obtained Specimens were examined by fluorescence microscopy, nucleic acid amplification tests (COBAS TaqMan, GenoType MTBDRplus assay and Xpert® MTB/RIF introduced step by step into the laboratory procedures), and cultured using Coletsos medium and the BACTEC MGIT 960
Comparator	*Induced sputum* 3 specimens collected on consecutive days Performed 4 hours after gastric lavage, prior to lunch To prevent the risk of bronchospasm induced by hypertonic saline, children were pre-treated with nebulized salbutamol (0.03 ml/kg, maximum 1 ml (1 ml = 5 mg)); subsequently, 5 ml of 5% sterile saline at a flow rate of 5 l per minute was nebulized for 15 minutes, followed by chest percussion on the front and back chest wall After this procedure, if spontaneous expectoration was not achieved, sputum was obtained by suctioning through the nasopharynx with a sterile mucus extractor Specimens were examined by fluorescence microscopy, NAATs (COBAS TaqMan, GenoType MTBDRplus assay and Xpert® MTB/RIF introduced step by step into the laboratory procedures), and cultured using Coletsos medium and the BACTEC MGIT 960
Location	Madrid, Spain
Outcomes measures and effect size	Culture positivity (number positive/total number participants) Cumulative yield for all 3 specimens (days 1 to 3) • gastric lavage = 8/17 • induced sputum = 7/17 • gastric lavage plus induced sputum = 10/17

Bibliographic reference	Jiménez MR, Guillén Martín S, Prieto Tato LM, Cacho Calvo JB, Alvarez García A, Soto Sánchez B and Ramos Amador JT (2013) Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infectious Diseases* 13(1): 222
	Cumulative yield for first 2 specimens (days 1 and 2) • gastric lavage = 7/17 • induced sputum = 6/17 • gastric lavage plus induced sputum = 9/17 Yield for first specimen (day 1) • gastric lavage = 7/17 • induced sputum = 5/17 • gastric lavage plus induced sputum = 8/17
	Smear positivity (number positive/total number participants) Cumulative yield for all 3 specimens (days 1 to 3) • gastric lavage = 1/17 • induced sputum = 2/17
	NAAT positivity (number positive/total number participants) Cumulative yield for all 3 specimens (days 1 to 3) • gastric lavage = 2/17 • induced sputum = 3/17
	Adverse effects – only reported for induced sputum Of the 16 patients that showed potential adverse effects to sputum induction (a total of 48 procedures), no serious adverse reactions occurred during or after the procedure

Bibliographic reference	**Jiménez MR, Guillén Martín S, Prieto Tato LM, Cacho Calvo JB, Alvarez García A, Soto Sánchez B and Ramos Amador JT (2013) Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infectious Diseases* 13(1): 222**
	The most common adverse events were mild epistaxis in 8 procedures (16.6%), nausea in 3 (6.25%) and increased coughing in 3 (6.25%) Only 1 infant had transient hypoxemia in 2 procedures (lowest oxygen saturation 87%) recovered spontaneously There were no episodes of bronchospasm
Source of funding	Funded in part by the Foundation for Research and Prevention of AIDS in Spain
Comments	
Abbreviations: NAATs, nucleic acid amplification tests	

1.1.10 Lloyd, 1968

Bibliographic reference	**Lloyd AV (1968) Bacteriological diagnosis of tuberculosis in children: a comparative study of gastric lavage and laryngeal swab methods. *East African Medical Journal* 45(3): 140-3**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes*

Bibliographic reference	**Lloyd AV (1968) Bacteriological diagnosis of tuberculosis in children: a comparative study of gastric lavage and laryngeal swab methods. *East African Medical Journal* 45(3): 140-3**
	Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 60
Patient characteristics	*Inclusion* Children *Characteristics of included population* Age ranged from 5 months to 6 years 5 had miliary tuberculosis, 6 had tuberculous meningitis, 4 had abdominal tuberculosis, 3 had spinal caries and the remainder had pulmonary lesions, either bronchopneumonia, segmental lesions or cavitation
Intervention	*Laryngeal swab*

Bibliographic reference	**Lloyd AV (1968) Bacteriological diagnosis of tuberculosis in children: a comparative study of gastric lavage and laryngeal swab methods. *East African Medical Journal* 45(3): 140-3**
	3 specimens collected, as far as possible, on 3 consecutive days The swabs were made of stainless steel wire The child was held firmly by its mother and its tongue brought forward with a tongue depressor The swab was dipped in sterile water before being inserted into the larynx If the child was old enough to understand, he was asked to cough, otherwise the tickling of the swab against the back of the throat was almost always sufficient to produce a cough Specimens were cultured on Löwenstein-Jensen medium
Comparator	*Gastric lavage* 3 specimens collected, as far as possible, on 3 consecutive days, in the early morning before food was given Specimens were cultured on Löwenstein-Jensen medium
Location	Kampala, Uganda
Outcomes measures and effect size	Culture positivity (number positive /total number of cases; note: all participants considered to have tuberculosis) Taking into account all 3 specimens • gastric lavage = 17/60 • laryngeal swab = 38/60 Taking into account first 2 specimens • gastric lavage = 4/60 • laryngeal swab = 15/60 Taking into account first specimen • gastric lavage = 1/60

Bibliographic reference	**Lloyd AV (1968) Bacteriological diagnosis of tuberculosis in children: a comparative study of gastric lavage and laryngeal swab methods. *East African Medical Journal* 45(3): 140-3**
	• laryngeal swab = 6/60
Source of funding	Supported by grants from Makerere University College and the East African Medical Research Council
Comments	

1.1.11 Maciel, 2010

Bibliographic reference	**Maciel EL, Peres RL, do Prado TN, Macedo CR, Palaci M, Vinhas SA, Dietze R, Johnson JL and Struchiner CJ (2010) Saline nebulization before gastric lavage in the diagnosis of pulmonary tuberculosis in children and adolescents. *Journal of Tropical Pediatrics* 56(6): 458-9**
Study type	Randomised controlled trial
Study quality	*Study limitations* Appropriate method of randomisation? *unclear* Adequate allocation concealment? *unclear* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded to intervention? *unclear* Investigators blinded to confounding and prognostic factors? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Intent-to-treat principle adhered to? *yes*

Bibliographic reference	**Maciel EL, Peres RL, do Prado TN, Macedo CR, Palaci M, Vinhas SA, Dietze R, Johnson JL and Struchiner CJ (2010) Saline nebulization before gastric lavage in the diagnosis of pulmonary tuberculosis in children and adolescents. *Journal of Tropical Pediatrics* 56(6): 458-9**
	Inconsistency Groups comparable at baseline? *yes, although details provided were limited* Groups received the same care apart from the intervention(s) studied? *yes, although details provided were limited* Equal follow-up? *yes* Groups equivalent for intervention completion? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Randomised = 104 participants • gastric lavage plus nebulisation = 36 • gastric lavage alone = 68
Patient characteristics	*Inclusion* Children with suspected pulmonary tuberculosis based on having a cough for >28 days and meeting one of the following criteria: household contact with a person with tuberculosis; weight loss or failure to gain weight; positive tuberculin skin test; or a chest radiograph with a parenchymal infiltrate, atelectasis, pleural effusion or lymphadenopathy *Exclusion* Previously treatment for tuberculosis HIV infection *Characteristics of included participants* Mean age and sex of subjects did not differ between groups

Bibliographic reference	**Maciel EL, Peres RL, do Prado TN, Macedo CR, Palaci M, Vinhas SA, Dietze R, Johnson JL and Struchiner CJ (2010) Saline nebulization before gastric lavage in the diagnosis of pulmonary tuberculosis in children and adolescents. *Journal of Tropical Pediatrics* 56(6): 458-9**
Intervention	*Gastric lavage plus nebulisation* Inhalation of 30 ml of nebulized sterile 3% hypertonic saline using an ultrasonic nebulizer for 30 minutes before gastric lavage After the gastric contents were aspirated and transferred to container with 10% disodium phosphate buffer and processed using standard procedures
Comparator	*Gastric lavage alone* Gastric contents were aspirated and transferred to container with 10% disodium phosphate buffer and processed using standard procedures
Location	Brazil
Outcomes measures and effect size	Sample volume (mean, ml) • gastric lavage plus nebulisation (n = 36) = 25 • gastric lavage alone (n = 68) = 10
	Culture positivity (number positive/total number of cases) • gastric lavage plus nebulisation = 9/36 • gastric lavage alone = 14/68
Source of funding	Supported by the Tuberculosis Research Unit at Case Western Reserve University, established with funds from the United States National Institute of Allergy and Infectious Diseases, National Institutes of Health, and, in part, by funding for CNPq (National Council for Scientific and Technological Development) and REDE-TB (Brazilian Tuberculosis Research Network)
Comments	

1.1.12 Menon, 2011

Bibliographic reference	**Menon PR, Lodha R, Singh U and Kabra SK (2011) A prospective assessment of the role of bronchoscopy and bronchoalveolar lavage in evaluation of children with pulmonary tuberculosis. *Journal of Tropical Pediatrics* 57(5): 363-7**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes*

Bibliographic reference	**Menon PR, Lodha R, Singh U and Kabra SK (2011) A prospective assessment of the role of bronchoscopy and bronchoalveolar lavage in evaluation of children with pulmonary tuberculosis. *Journal of Tropical Pediatrics* 57(5): 363-7**
	Did the study avoid inappropriate exclusions? *yes* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *unclear* Equal follow-up? *unclear* Groups comparable for availability of data? *unclear* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 52
Patient characteristics	*Inclusion*

Bibliographic reference	**Menon PR, Lodha R, Singh U and Kabra SK (2011) A prospective assessment of the role of bronchoscopy and bronchoalveolar lavage in evaluation of children with pulmonary tuberculosis. *Journal of Tropical Pediatrics* 57(5): 363-7**
	Children <16 years of age with probably pulmonary tuberculosis, based on the presence of cough (≥2 weeks), fever and persistent radiological infiltrates (chest x-ray showing atelectasis, consolidation, cavitations or effusion *Exclusion* Antituberculosis prophylaxis or treatment HIV infection Respiratory failure *Characteristics of included participants* Age (mean±SD (range), years) = 7.8±3.93 (0.75–16) 22 females, 30 males 38 (73%) of children had cough of >2 weeks Positive Mantoux (n = 34) = 27 (65.4%) Chest roentography: • mediastinal adenopathy = 11 • cavity = 5 • consolidation = 13 • parenchymal infiltrates = 23
Intervention	*Nasogastric aspiration* All participants provided a minimum of 1 specimen After an overnight fast of at least 6 hours, nasogastric tube was passed before the child got up and the gastric contents aspirated

Bibliographic reference	**Menon PR, Lodha R, Singh U and Kabra SK (2011) A prospective assessment of the role of bronchoscopy and bronchoalveolar lavage in evaluation of children with pulmonary tuberculosis. *Journal of Tropical Pediatrics* 57(5): 363-7**
	If the aspirate was <10 ml, normal saline (10 ml) was injected in the tube, left for 2 to 3 minutes and then aspirated until at least 10 ml of aspirate was obtained Examined by Ziehl-Neelsen microscopy
Comparator	*Bronchoalveolar lavage* All participants provided 1 specimen Performed using a flexible fibreoptic bronchoscope Intravenous midazolam (0.15 mg/kg) and pethidine (1 to 2 mg/kg) were used in all patients Atropine (0.01 mg/kg, at a minimum dose of 0.1 mg) prior to the procedure Lignocaine 2% jelly was used in the nostril, and 1% lignocaine was sprayed over the vocal cords on visualisation The flexible bronchoscope was passed through the roomier nostril, and oxygen was given through the other Lavage was performed with sterile 0.9% saline (2 to 3 ml/kg, at a minimum of 10 ml) from the radiologically affected segment or lesion Examined by Ziehl-Neelsen microscopy
Location	New Delhi, India
Outcomes measures and effect size	Smear positivity (number positive/total cases) • nasogastric aspiration = 6/52 • bronchoalveolar lavage = 16/52 • nasogastric aspiration plus bronchoalveolar lavage = 19/52
Source of funding	No details provided

Bibliographic reference	**Menon PR, Lodha R, Singh U and Kabra SK (2011) A prospective assessment of the role of bronchoscopy and bronchoalveolar lavage in evaluation of children with pulmonary tuberculosis. *Journal of Tropical Pediatrics* 57(5): 363-7**
Comments	Incomplete data for 2nd and 3rd gastric aspirations (n = 22) therefore data not extracted
Abbreviations: SD, standard deviation	

1.1.13 Mukherjee, 2013

Bibliographic reference	**Mukherjee A, Singh S, Lodha R, Singh V, Hesseling AC, Grewal HM and Kabra SK; Delhi Pediatric TB Study Group (2013) Ambulatory gastric lavages provide better yields of Mycobacterium tuberculosis than induced sputum in children with intrathoracic tuberculosis. *Pediatric Infectious Disease Journal* 32(12): 1313-7**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *yes* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes, same day* *Inconsistency*

Bibliographic reference	**Mukherjee A, Singh S, Lodha R, Singh V, Hesseling AC, Grewal HM and Kabra SK; Delhi Pediatric TB Study Group (2013) Ambulatory gastric lavages provide better yields of Mycobacterium tuberculosis than induced sputum in children with intrathoracic tuberculosis. *Pediatric Infectious Disease Journal* 32(12): 1313-7**
	Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 403 participants
Patient characteristics	*Inclusion* Children aged 6 months to 15 years with newly diagnosed intrathoracic tuberculosis, based on clinico-radiological criteria as recommended by the Indian Academy of Pediatrics; in the presence of persistent radiological abnormalities, with nonresolution of clinical symptoms and no alternative cause for symptoms and radiological findings, a clinical diagnosis of probable intrathoracic tuberculosis was made *Exclusion* Known HIV infection *Characteristics of the included population* Female = 56.6% Age (median [interquartile range], months) = 111 [68–144] History of contact with adult tuberculosis case = 150 (37.2%) Positive tuberculin skin test = 371 (92.1%) Primary pulmonary complex on chest radiograph = 120 (29.8%) Pleural effusion on chest radiograph = 54 (13.4%)
Intervention	*Nasogastric aspiration and lavage* Specimens collected on 2 consecutive days after overnight fasting of 6–8 hours An appropriate sized feeding tube was inserted through nostril till it reached the stomach; the gastric contents were aspirated

Bibliographic reference	**Mukherjee A, Singh S, Lodha R, Singh V, Hesseling AC, Grewal HM and Kabra SK; Delhi Pediatric TB Study Group (2013) Ambulatory gastric lavages provide better yields of Mycobacterium tuberculosis than induced sputum in children with intrathoracic tuberculosis. *Pediatric Infectious Disease Journal* 32(12): 1313-7**
	completely followed by a gastric lavage with 5–10 mL of sterile saline Samples were transported to laboratory for processing within 1–2 hours Specimens were examined by Ziehl-Neelsen staining and cultured for 6 weeks on the BACTEC MGIT 960 system
Comparator	*Sputum induction plus nasopharyngeal aspiration* Specimens collected on 2 consecutive days after overnight fasting of 6–8 hours; during the same session, and approximately 30 minutes after collecting gastric lavage, induced sputum was also collected from each patient The child was administered 2 puffs (100 µg/puff) of salbutamol inhalation by metered dose inhaler followed by nebulization with 3 mL of 3% saline over next 15–20 minutes; chest physiotherapy was performed, and then a feeding tube of appropriate size was placed in the nostril till it reached the posterior nasopharyngeal wall, which was then used to aspirate the secretions The usual volume of sample collected was 1–2 ml Specimens were examined by Ziehl-Neelsen staining and cultured for 6 weeks on the BACTEC MGIT 960 system
Location	Delhi, India
Outcomes measures and effect size	Culture positivity (number of positive cases) • nasogastric aspiration and lavage = 135/403 • sputum induction plus nasopharyngeal aspiration = 72/403 *Day 1* / *Day 2* / *Day 1 or 2* Nasogastric aspiration and lavage: 91 / 101 / 135 Sputum induction plus nasopharyngeal aspiration: 48 / 53 / 72 Smear positivity (number of positive cases) • nasogastric aspiration and lavage = 42/403 • sputum induction plus nasopharyngeal aspiration = 23/403 *Day 1* / *Day 2* / *Day 1 or 2* Nasogastric aspiration and lavage: 28 / 25 / 42 Sputum induction plus nasopharyngeal aspiration: 14 / 16 / 23 Smear and/or culture positivity (number of positive cases) • nasogastric aspiration and lavage = 79/403 • sputum induction plus nasopharyngeal aspiration = 135/403 K statistic = 0.441

Bibliographic reference	**Mukherjee A, Singh S, Lodha R, Singh V, Hesseling AC, Grewal HM and Kabra SK; Delhi Pediatric TB Study Group (2013) Ambulatory gastric lavages provide better yields of Mycobacterium tuberculosis than induced sputum in children with intrathoracic tuberculosis. *Pediatric Infectious Disease Journal* 32(12): 1313-7**
	Agreement = 77.7% *Day 1* / *Day 2* / *Day 1 or 2* Nasogastric aspiration and lavage: 95 / 103 / 135 Sputum induction plus nasopharyngeal aspiration: 52 / 57 / 79
	Adverse events Both gastric lavage and sputum induction were carried out without any clinically significant adverse events Minor events encountered were 4 (0.5%) episodes of vomiting and 8 (1%) episodes of nasal bleed during gastric lavage; 2 (0.25%) episodes each of vomiting and cough during sputum induction
Source of funding	No details provided
Comments	

1.1.14 Oberhelman, 2006

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Caviedes L, Castillo ME, Kissinger P, Moore DA, Evans C and Gilman RH (2006) Improved recovery of Mycobacterium tuberculosis from children using the microscopic observation drug susceptibility method. *Pediatrics* 118(1):e100-6**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *yes* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes, although details provided were limited* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear*

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Caviedes L, Castillo ME, Kissinger P, Moore DA, Evans C and Gilman RH (2006) Improved recovery of Mycobacterium tuberculosis from children using the microscopic observation drug susceptibility method. *Pediatrics* 118(1):e100-6**
	Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 165 participants • nasogastric aspirate = 324 specimens • nasopharyngeal aspirate = 319 specimens
Patient characteristics	*Inclusion* Children aged ≤12 years Clinical suspicion of tuberculosis, defined as a Stegen-Toledo clinical score ≥5 points[a] Absence of antituberculosis therapy *Characteristics of included participants* Approximately 20% of patients were inpatients, and 80% were outpatients 93 boys and 72 girls

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Caviedes L, Castillo ME, Kissinger P, Moore DA, Evans C and Gilman RH (2006) Improved recovery of Mycobacterium tuberculosis from children using the microscopic observation drug susceptibility method. *Pediatrics* 118(1):e100-6**
	Mean age of all patients was 4.6 years, and the age distribution of each group was as follows: • ≤1 year = 21 (12%) patients • 1 to 5 years = 72 (44%) patients • >5 years = 72 (44%) patients HIV enzyme-linked immunosorbent assay results were negative in 136 (82%) patients, and the test was declined in 29 (18%) patients, none of whom had clinical evidence of HIV infection
Intervention	*Nasogastric aspirate* Collected on 2 successive mornings by nasogastric intubation; the volume of the specimens was augmented as needed by injection of sterile water Examined by fluorescence microscopy, and cultured by Microscopic Observation Drug Susceptibility and Löwenstein-Jensen techniques
Comparator	*Nasopharyngeal aspirate* Collected daily for 2 consecutive days by insertion of a soft, flexible nasopharyngeal tube into the nasopharynx, lavage with 5 mL of saline, and aspiration of the respiratory secretions into a container with an electrical suction device or hand-held aspirator Examined by fluorescence microscopy, and cultured by Microscopic Observation Drug Susceptibility and Löwenstein-Jensen techniques
Location	Lima, Peru
Outcomes measures and effect size	Löwenstein-Jensen positivity (number positive/total number of cases) • nasogastric aspirate = 11/321 • nasopharyngeal aspirate = 8/314
	Microscopic Observation Drug Susceptibility positivity (number positive/total number of cases) • nasogastric aspirate = 19/321 • nasopharyngeal aspirate = 11/314
	Fluorescence microscopy positivity (number positive/total number of cases) • nasogastric aspirate = 8/321 • nasopharyngeal aspirate = 4/314
Source of funding	Financially supported by the National Institutes of Health and the National Institute of Allergy and Infectious Diseases
Comments	
[a] Stegen-Toledo criteria (note: although positive *M. tuberculosis* culture is 1 of the Stegen-Toledo clinical criteria, culture results are the primary outcome parameter of the study, and these were not available at enrollment, so this criterion was not used to determine patient eligibility):	

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Caviedes L, Castillo ME, Kissinger P, Moore DA, Evans C and Gilman RH (2006) Improved recovery of Mycobacterium tuberculosis from children using the microscopic observation drug susceptibility method. *Pediatrics* 118(1):e100-6**

Finding	Score
Positive culture	7
TB granuloma	4
Positive purified protein derivative >10 mm	3
Known contact in the last 2 y	2
Suggestive radiograph	2
Suggestive clinical picture (cough >2 wk)	2
Clinical criteria	
Highly probable TB: score ≥7	
Probable TB: score 5–6	
Suspicious TB: score 3–4	
Unlikely TB: score 0–2	

1.1.15 Oberhelman, 2010

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Gilman RH, Caviedes L, Castillo ME, Kolevic L, Del Pino T, Saito M, Salazar-Lindo E, Negron E, Montenegro S, Laguna-Torres VA, Moore DA and Evans CA (2010) Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. *Lancet Infectious Diseases* 10(9): 612-20**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes, though only because control data not extracted (gastric aspiration not performed in these as procedure too invasive to be justified in healthy individuals)* Did the study avoid inappropriate exclusions? *yes* Participants blinded? *unclear* Individuals administering care blinded? *unclear*

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Gilman RH, Caviedes L, Castillo ME, Kolevic L, Del Pino T, Saito M, Salazar-Lindo E, Negron E, Montenegro S, Laguna-Torres VA, Moore DA and Evans CA (2010) Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. *Lancet Infectious Diseases* 10(9): 612-20**
	Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *unclear* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 218
Patient characteristics	*Inclusion* Clinical evidence suggestive of pulmonary tuberculosis (Stegen-Toledo score[a] ≥ 5 points) Age ≤12 years

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Gilman RH, Caviedes L, Castillo ME, Kolevic L, Del Pino T, Saito M, Salazar-Lindo E, Negron E, Montenegro S, Laguna-Torres VA, Moore DA and Evans CA (2010) Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. *Lancet Infectious Diseases* 10(9): 612-20**
	Absence of antituberculosis therapy *Exclusion* Children with evidence of HIV infection or AIDS
Intervention	*Nasogastric aspirate* Gastric aspirates were collected on 2 successive early mornings by brief (<10 minute) nasogastric intubation following an overnight fast The volume of gastric aspirates was augmented as needed by injecting 5 ml. sterile water and aspirating back Examined by IS6110-based PCR, and cultured by Microscopic Observation Drug Susceptibility and Löwenstein-Jensen techniques
Comparator	*Nasopharyngeal aspirate* Nasopharyngeal aspirates were collected daily for 2 days by inserting a soft flexible nasopharyngeal tube into the nasopharynx, lavaging with 5 ml of saline solution, and aspirating with an electrical suction device or hand-held aspirator; the procedure induces a cough and sputum production, which is then aspirated from the nasopharynx Examined by IS6110-based PCR, and cultured by Microscopic Observation Drug Susceptibility and Löwenstein-Jensen techniques
Location	Peru
Outcomes measures and effect size	Culture positivity (number of positives/ total cases) • nasogastric aspirate = 22/216 • nasopharyngeal aspirate = 12/215
	PCR positivity (number of positives/ total cases)

Bibliographic reference	**Oberhelman RA, Soto-Castellares G, Gilman RH, Caviedes L, Castillo ME, Kolevic L, Del Pino T, Saito M, Salazar-Lindo E, Negron E, Montenegro S, Laguna-Torres VA, Moore DA and Evans CA (2010) Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. *Lancet Infectious Diseases* 10(9): 612-20**
	• nasogastric aspirate = 35/217 • nasopharyngeal aspirate = 26/218
Source of funding	Supported by the National Institutes of Health, NIAID, IFHAD, FIND and the Wellcome Trust
Comments	

[a] Stegen-Toledo criteria (note: although positive *M. tuberculosis* culture is 1 of the Stegen-Toledo clinical criteria, culture results are the primary outcome parameter of the study, and these were not available at enrollment, so this criterion was not used to determine patient eligibility):

Finding	Score
Positive culture	7
TB granuloma	4
Positive purified protein derivative >10 mm	3
Known contact in the last 2 y	2
Suggestive radiograph	2
Suggestive clinical picture (cough >2 wk)	2
Clinical criteria	
Highly probable TB: score ≥7	
Probable TB: score 5–6	
Suspicious TB: score 3–4	
Unlikely TB: score 0–2	

1.1.16 Owens, 2007

Bibliographic reference	**Owens S, Abdel-Rahman IE, Balyejusa S, Musoke P, Cooke RP, Parry CM and Coulter JB (2007) Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. *Archives of Disease in Childhood* 92(8): 693-6**
Study type	Cross-sectional
Study quality	*Study limitations*

Bibliographic reference	**Owens S, Abdel-Rahman IE, Balyejusa S, Musoke P, Cooke RP, Parry CM and Coulter JB (2007) Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. *Archives of Disease in Childhood* 92(8): 693-6**
	Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *smear positivity, yes; culture positivity, unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	96 eligible for inclusion; 94 participants included A child with AIDS had dyspnoea and pneumonic changes on chest radiograph; he deteriorated during pre-induction with

Bibliographic reference	Owens S, Abdel-Rahman IE, Balyejusa S, Musoke P, Cooke RP, Parry CM and Coulter JB (2007) Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. *Archives of Disease in Childhood* 92(8): 693-6
	salbutamol and the procedure was abandoned Another child who became emotionally distressed during nasopharyngeal aspiration developed a brisk epistaxis and the procedure was abandoned Both children were excluded from analysis because their datasets were incomplete Six cultures were contaminated and not included in the paired analysis for culture positivity
Patient characteristics	*Inclusion* Symptoms suggestive of pulmonary tuberculosis , for example cough for over 2 weeks, weight loss, or severe malnutrition not responding to nutritional rehabilitation Positive tuberculin test (≥10 mm induration, irrespective of the presence of a BCG scar, was regarded as positive; in severely malnourished patients or patients known to have HIV infection, 6–9 mm was accepted) and/or a chest radiograph compatible with tuberculosis (hilar or mediastinal lymphadenopathy, local collapse/consolidation, severe bilateral but asymmetric disease, cavitation or miliary changes) Where the tuberculin test was negative and the chest radiograph was non-specific, the child was given a 2 week course of antibiotics. If symptoms or chest radiograph did not improve, they were then recruited *Characteristics of included participants* Median (range) age of the study group was 48 (4–144) months 57 (60.6%) were male Median weight-for-height z score (interquartile range) was −1.30 (−2.79 to +0.04) 22.9% were severely malnourished Of 63 children who were tested, 44 (69.8%) were infected with HIV
Intervention	*Nasopharyngeal aspiration* Single specimen collected; collection performed prior to sputum induction Patients were in the sitting position; a graduated suction catheter was inserted through the nostril into the oropharynx which stimulated a cough reflex; secretions were aspirated mechanically Sputum specimens were digested and decontaminated with NAOH-NALC-NA-citrate before undergoing centrifugation, fluorescence microscopy (the presence of 1 acid-fast bacillus in 100 high-powered microscopy fields defined a positive smear) and culture on Löwenstein Jensen media
Comparator	*Sputum induction plus nasopharyngeal aspiration* Single specimen collected; collection performed after nasopharyngeal aspiration Salbutamol (500 µg) was nebulised initially for 5 min; this was followed by 15 ml of 3% hypertonic saline for 20 min Nasopharyngeal aspiration was undertaken to obtain the secretions Chest physiotherapy was not undertaken prior to suction Sputum specimens were digested and decontaminated with NAOH-NALC-NA-citrate before undergoing centrifugation,

Bibliographic reference	**Owens S, Abdel-Rahman IE, Balyejusa S, Musoke P, Cooke RP, Parry CM and Coulter JB (2007) Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. *Archives of Disease in Childhood* 92(8): 693-6**
	fluorescence microscopy (the presence of 1 acid-fast bacillus in 100 high-powered microscopy fields defined a positive smear) and culture on Löwenstein Jensen media
Location	Kampala, Uganda
Outcomes measures and effect size	Culture positivity • nasopharyngeal aspiration = 21/88 • sputum induction plus nasopharyngeal aspiration = 19/88 K statistic = 0.74
	Smear positivity • nasopharyngeal aspiration = 8/94 • sputum induction plus nasopharyngeal aspiration = 9/94 K statistic =0.81
	Adverse events A small number of children had coughing spasms and/or vomiting after sputum induction Some had bloodstained aspirates following both procedures
Source of funding	No details provided
Comments	

1.1.17 Planting, 2014

Bibliographic reference	**Planting NS, Visser GL, Nicol MP, Workman L, Isaacs W and Zar HJ (2014) Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 18(1): 8-12**
Study type	Cohort
Study quality	*Study limitations* Method of allocation was unrelated to potential confounding factors? *no, based on child's ability to spontaneously produce sputum* Attempts were made within the design or analysis to balance the comparison groups for potential confounders? *no*

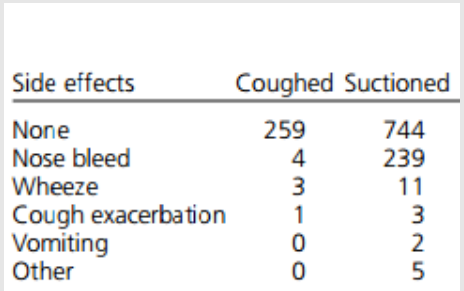
Bibliographic reference	**Planting NS, Visser GL, Nicol MP, Workman L, Isaacs W and Zar HJ (2014) Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 18(1): 8-12**
	Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* *Inconsistency* Groups comparable at baseline? *unclear* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	A total of 1270 sputum induction procedures were performed in 690 patients • induced sputum plus nasopharyngeal aspiration = 993 • coughed induced sputum = 264 • unknown = 13
Patient characteristics	*Inclusion*

Bibliographic reference	**Planting NS, Visser GL, Nicol MP, Workman L, Isaacs W and Zar HJ (2014) Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 18(1): 8-12**
	Children hospitalised with suspected pulmonary tuberculosis based on chronic cough (>14 days) and one of the following criteria: household contact known to be infected with tuberculosis within the last 3 months; weight loss or failure to gain weight in the previous 3 months; positive tuberculin skin test; suggestive features on chest radiography *Exclusion* ≥72 hours of antituberculosis treatment or prophylaxis *Characteristics of included participants*

	Total (N = 690) median [IQR] or n (%)
Age, months	27.3 [13.4 to 64.2]
Age group, months	
<12	146 (21.2)
12-60	356 (51.6)
>60	188 (27.2)
Sex, male	368 (53.3)
HIV infection	
Infected	164 (23.8)
Non-infected	525 (76.1)
Unknown	1 (0.1)
Total IS procedures	1270
IS1	690
IS2	580
Height-for-age	−1.3 [−2.3 to −0.3]
Malnourished	175 (25.4)
Weight-for-age	−1.4 [−2.7 to −0.4]
Weight/height-for-age	−0.5 [−1.9 to 0.5]
Patients presenting with	
Oxygen saturation, %	98 [96 to 99]
Receiving supplemental oxygen	33 (4.8)
Respiratory rate, bpm	36 [28 to 45]
Subcostal recession	115 (16.7)
Wheeze	95 (13.8)

IQR = interquartile range; IS = induced sputum; bpm = breaths per minute.

Intervention	*Induced sputum plus nasopharyngeal aspiration*

Bibliographic reference	**Planting NS, Visser GL, Nicol MP, Workman L, Isaacs W and Zar HJ (2014) Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 18(1): 8-12**
	2 specimens collected Sputum induction was performed after 2 to 3 hours of fasting Children were pre-treated with 200 µg salbutamol via a metered dose inhaler with attached spacer to prevent bronchoconstriction A jet nebuliser attached to oxygen at a flow rate of 5 l/min delivered 5 ml 5% sterile saline solution for 15 minutes Suctioning was performed through the nasopharynx with a sterile mucus extractor Specimens were cultured for 6 weeks on the BACTEC MGIT 960
Comparator	*Coughed induced sputum* 2 specimens collected Sputum induction was performed after 2 to 3 hours of fasting Children were pre-treated with 200 µg salbutamol via a metered dose inhaler with attached spacer to prevent bronchoconstriction A jet nebuliser attached to oxygen at a flow rate of 5 l/min delivered 5 ml 5% sterile saline solution for 15 minutes Children were encouraged to cough, and the expectorated sputum sample was collected Specimens were cultured for 6 weeks on the BACTEC MGIT 960
Location	Cape Town, South Africa
Outcomes measures and effect size	Culture positivity(number positive/total number of specimens obtained by collection method) • induced sputum plus nasopharyngeal aspiration = 129/993 • coughed induced sputum = 62/264
	Adverse events 
Source of funding	Funded by the National Institutes for Health, USA, the National Health Laboratory Services Research Trust, the Medical Research Council of South Africa and the National Research Foundation, South Africa
Comments	

Side effects	Coughed	Suctioned
None	259	744
Nose bleed	4	239
Wheeze	3	11
Cough exacerbation	1	3
Vomiting	0	2
Other	0	5

1.1.18 Somu, 1995

Bibliographic reference	**Somu N, Swaminathan S, Paramasivan CN, Vijayasekaran D, Chandrabhooshanam A, Vijayan VK and Prabhakar R (1995) Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. *Tubercle and Lung Disease* 76(4): 295-9**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes, same day or the following morning* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes*

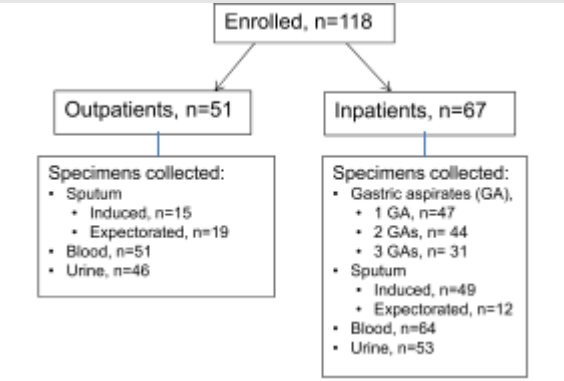
Bibliographic reference	**Somu N, Swaminathan S, Paramasivan CN, Vijayasekaran D, Chandrabhooshanam A, Vijayan VK and Prabhakar R (1995) Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. *Tubercle and Lung Disease* 76(4): 295-9**
	Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 50 participants
Patient characteristics	*Inclusion* Children (age group 7 months to 12 years) presenting with signs and symptoms suggestive of pulmonary TB who had a radiographic abnormality but were not acutely sick Parenchymal lesion on the chest X-ray that did not clear after 3 weeks in spite of antibiotics No prior antituberculosis treatment *Characteristics of included participants* Mean age = 5.1 years (range 7 months to 12 years) 27 males and 23 females The majority of the patients were malnourished with 33 of the 50 (66%) suffering from second or third degree malnutrition (Gomez classification) The commonest radiographic abnormality was a persistent consolidation with or without hilar lymphadenopathy (25 cases), followed by bronchiectatic changes in one or both lower lobes (10 cases); hilar or mediastinal adenopathy alone was seen in 6 cases, 5 children had evidence of cavitation in addition to parenchymal changes, 1 had collapse consolidation and 3 had segmental atelectasis The Mantoux test was positive (> 10 ram) in 37 patients and negative in 13 of the 50 children (26%) A history of contact with an adult tuberculosis patient was elicited in 21 (42%) children
Intervention	*Nasogastric lavage* Performed early in the morning, after an overnight fast

Bibliographic reference	**Somu N, Swaminathan S, Paramasivan CN, Vijayasekaran D, Chandrabhooshanam A, Vijayan VK and Prabhakar R (1995) Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. *Tubercle and Lung Disease* 76(4): 295-9**
	A nasogastric tube was used to aspirate the gastric contents, after which 5-10 ml normal saline was injected through the nasogastric tube and, again, aspirated Specimens were cultured for 6 to 8 weeks on 2 slopes each of Löwenstein-Jensen medium, Löwenstein-Jensen medium with sodium pyruvate and Middlebrooks selective 7HII medium and 2 bottles of selective Kirschner's liquid medium
Comparator	*Bronchoalveolar lavage* Performed using a flexible fibreoptic bronchoscope The patients were kept fasting overnight Topical anaesthesia with 2% Xylocaine was applied to the nose, larynx and upper airways as the bronchosope was advanced; the amount of Xylocaine used ranged 3-5 ml (60-100 mg) The flexible bronchoscope was inserted transnasally, advanced into the trachea and wedged into the most involved segment as seen on chest X-ray or the nearest segment possible Bronchoalveolar lavage was performed by instilling 2 ml/kg sterile normal saline and subsequently aspirating it back into a specimen trap, using a suction apparatus Specimens were cultured for 6 to 8 weeks on 2 slopes each of Löwenstein-Jensen medium, Löwenstein-Jensen medium with sodium pyruvate and Middlebrooks selective 7HII medium and 2 bottles of selective Kirschner's liquid medium
Location	Madras, India
Outcomes measures and effect size	Culture positivity • nasopharyngeal lavage = 16/50 • bronchoalveolar lavage = 6/50
Source of funding	No details provided
Comments	

1.1.19 Thomas, 2014

Bibliographic reference	**Thomas TA, Heysell SK, Moodley P, Montreuil R, Ha X, Friedland G, Bamber SA, Moll AP, Gandhi N, Brant WE, Sturm W and Shah S (2014) Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infectious Diseases* 14: 11**
Study type	Cross-sectional

Bibliographic reference	**Thomas TA, Heysell SK, Moodley P, Montreuil R, Ha X, Friedland G, Bamber SA, Moll AP, Gandhi N, Brant WE, Sturm W and Shah S (2014) Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infectious Diseases* 14: 11**
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes* Participants blinded? *unclear* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes*

Bibliographic reference	**Thomas TA, Heysell SK, Moodley P, Montreuil R, Ha X, Friedland G, Bamber SA, Moll AP, Gandhi N, Brant WE, Sturm W and Shah S (2014) Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infectious Diseases* 14: 11**
	Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 118 
Patient characteristics	*Inclusion* Tuberculosis suspects aged ≥6 months and ≤12 years Subjects were new tuberculosis suspects or had persistent symptoms despite ≥2 months of antituberculosis treatment Patients were eligible if they had at least one of the following: chronic cough, failure to improve after pneumonia treatment, contact with a tuberculosis case, failure to thrive, painless superficial lymphadenopathy, signs of meningitis which were not responsive to antibiotics, or chest radiograph suggestive of tuberculosis *Exclusion* On antituberculosis treatment for >2 days, or recently defaulted on antituberculosis treatment *Characteristics of included participants*

Bibliographic reference	**Thomas TA, Heysell SK, Moodley P, Montreuil R, Ha X, Friedland G, Bamber SA, Moll AP, Gandhi N, Brant WE, Sturm W and Shah S (2014) Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infectious Diseases* 14: 11**

	Total n = 118, (%)
Age, mean years [SD]	4.7 [3.1]
Female gender, n (%)	53 (45)
Mother as primary caregiver	70 (59)
Either parent deceased	37 (31)
HIV-infected mother	50 (42)
Other HIV-infected family member	9 (8)
TB contact reported	62 (53)
Drug-resistant TB contact reported	4 (3)
Contact with "chronic cougher"	19 (16)
Prior TB	37 (31)
Prior hospitalization (≥1)	31 (26)
Malnourished	52 (44)
Severely malnourished (n, % of malnourished)	42 (81)
Tested for HIV	99 (84)
HIV positive	64 (65)
On HAART, n (% of HIV+)	32 (50)
CD4%, median [IQR]	16.8 [11.5-22.3]
Hemoglobin, median g/dL [IQR]	9.9 [8.8-11.2]
Albumin, median g/L [IQR]	32.0 [28.1-37.0]
Erythrocyte Sedimentation Rate, median [IQR]	32.0 [14.0-75.0]
Abnormal chest radiograph consistent with TB	84* (85)
Enrolled while failing ≥2 mo TB treatment	8 (7)
Started on TB treatment	59 (50)

*Of 99 children with chest radiographs available for review.

Intervention	*Nasogastric aspirate* 1 to 3 consecutive morning gastric aspirates were collected according to World Health Organisation guidance after an overnight fast and prior to sputum induction

Bibliographic reference	**Thomas TA, Heysell SK, Moodley P, Montreuil R, Ha X, Friedland G, Bamber SA, Moll AP, Gandhi N, Brant WE, Sturm W and Shah S (2014) Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infectious Diseases* 14: 11**
	An aliquot was used for fluorescent microscopic sputum examination for acid-fast bacilli and the remainder was split for parallel culture on Middlebrook 7H11 agar plates and automated broth culture via the BACTEC MGIT-960 system (solid cultures were monitored at 21- and 42-days; liquid cultures were monitored continuously for 42 days)
Comparator	*Induced or spontaneously produced sputum* Single sputum induction according to World Health Organisation guidance by the hospital's trained respiratory physiotherapists An aliquot was used for fluorescent microscopic sputum examination for acid-fast bacilli and the remainder was split for parallel culture on Middlebrook 7H11 agar plates and automated broth culture via the BACTEC MGIT-960 system (solid cultures were monitored at 21- and 42-days; liquid cultures were monitored continuously for 42 days)
Location	Tugela Ferry, South Africa
Outcomes measures and effect size	Culture positivity (number positive/ total number of cases) • nasogastric aspirate = 5/67 • sputum = 7/67 • nasogastric aspirate plus sputum = 8/67 Among the 5 children who were culture-positive by sequential gastric aspirates, the yield from the first gastric aspirate was equivalent to multiple collections
	Adverse effects – only reported for induced sputum Sputum induction was well tolerated overall: no child experienced prolonged respiratory distress, one child required brief supplemental oxygen and two had post-procedural vomiting
Source of funding	Supported in part by the Einstein-Montefiore Center for AIDS funded by the National Institutes of Health, the Burroughs Wellcome Fund/American Society of Tropical Medicine & Hygiene, the Howard Hughes Medical

Bibliographic reference	**Thomas TA, Heysell SK, Moodley P, Montreuil R, Ha X, Friedland G, Bamber SA, Moll AP, Gandhi N, Brant WE, Sturm W and Shah S (2014) Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infectious Diseases* 14: 11**
	Institute, the US President's Emergency Plan for AIDS Relief and the Doris Duke Charitable Foundation Clinical Scientist Development Award
Comments	

1.1.20 Zar, 2000

Bibliographic reference	**Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D and Hussey G (2000) Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Archives of Disease in Childhood* 82(4): 305-8**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *unclear* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes, sputum induction was performed on enrolment and gastric lavage was performed after a minimum four hour fast*

Bibliographic reference	**Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D and Hussey G (2000) Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Archives of Disease in Childhood* 82(4): 305-8**
	Inconsistency Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 142
Patient characteristics	*Inclusion* Children with a primary diagnosis of pneumonia and who were HIV infected, were suspected of having HIV infection or were admitted to the intensive care unit but were not intubated *Characteristics of included participants*

Bibliographic reference	**Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D and Hussey G (2000) Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Archives of Disease in Childhood* 82(4): 305-8**
	Characteristic / *Children without TB (n =126)* / *Children with TB (n = 16)* Age (months) 9 (3–21.5) 12 (7–25) Male:female 1.2 2.2 ICU admission, n (%) 18 (14) 2 (12) HIV positive, n (%) 90 (71) 10 (63) TB contact, n (%) 24 (19) 7 (44)* Use of supplemental O_2, n (%) 83 (66) 8 (50) Baseline O_2 saturation in air 94 (90.5–97) 93.5 (88–98) Baseline RR 50 (40–60) 53 (40–63.5) Continuous variables expressed as median (25th to 75th percentile). TB, tuberculosis; ICU, intensive care unit; RR, respiratory rate. *p = 0.02.
Intervention	*Nasogastric lavage* Early morning gastric lavage was performed after an overnight fast of at least 4 hours, ideally on 2 or 3 consecutive mornings A nasogastric tube was passed before the child arose and the gastric contents were aspirated Normal saline 20 ml was inserted down the tube, left for 2 to 3 minutes and then aspirated; additional 5 to 10 ml normal saline aliquots were inserted and aspirated until a minimum of 20 ml of aspirate was obtained Specimens were cultured for 6 weeks in a BACTEC 12B bottle containing supplemented Middlebrook medium
Comparator	*Induced sputum* Sputum induction was undertaken on the day of enrolment after a 2 to 3 hour fast Children were pretreated with 200 µg salbutamol given by a metered dose inhaler with attached spacer to prevent the occurrence of bronchial constriction A jet nebuliser attached to oxygen delivered 5 ml of 5% sterile saline for 15 minutes

Bibliographic reference	**Zar HJ, Tannenbaum E, Apolles P, Roux P, Hanslo D and Hussey G (2000) Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Archives of Disease in Childhood* 82(4): 305-8**
	Thereafter, physiotherapy techniques – including chest percussion, vibration, shaking and active cycle breathing – were applied Sputum was obtained either by expectoration (in children unable to cooperate) or by suctioning through the nasopharynx or oropharynx using a sterile mucus extractor Specimens were cultured for 6 weeks in a BACTEC 12B bottle containing supplemented Middlebrook medium
Location	Cape Town, South Africa
Outcomes measures and effect size	Culture positivity • nasogastric lavage = 9/142 • induced sputum = 15/142
Source of funding	Funded by the Medical Research Council of South Africa, the South African Pulmonology Society and the ICH Fund of the Red Cross Children's Hospital
Comments	

1.1.21 Zar, 2005

Bibliographic reference	**Zar HJ, Hanslo D, Apolles P, Swingler G and Hussey G (2005) Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 365(9454): 130-4**
Study type	Cross-sectional
Study quality	*Study limitations* Was a consecutive or random sample of patients enrolled? *unclear* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes*

Bibliographic reference	**Zar HJ, Hanslo D, Apolles P, Swingler G and Hussey G (2005) Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 365(9454): 130-4**
	Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes* *Inconsistency* Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* *Indirectness* Population matches population of interest? *yes* Intervention matches intervention of interest? *yes* Outcomes match the outcomes of interest? *yes*
Number of patients	Included = 250
Patient characteristics	*Inclusion* Suspected pulmonary tuberculosis on the basis of a chronic cough (more than 28 days) and one of the following

Bibliographic reference	**Zar HJ, Hanslo D, Apolles P, Swingler G and Hussey G (2005) Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 365(9454): 130-4**
	criteria: household contact known to be infected with tuberculosis within the previous 3 months; loss of weight or failure to gain weight within the previous 3 months; positive skin test to purified protein derivative, or chest radiography with parenchymal infiltrate, atelectasis, pleural effusion, or lymphadenopathy *Exclusion* Taking treatment for tuberculosis, had completed such treatment within the past 2 weeks, or were taking prophylaxis for this disease Had signs of upper airway obstruction Had an arterial oxygen saturation less than 92% in room air *Characteristics of included participants* 141 (56%) were male Median age was 13 months (interquartile range 6 to 24) Baseline median respiratory rate of children was 56 (interquartile range 40 to 64) breaths per minute Median arterial oxygen saturation was 96% (interquartile range 95 to 98%) 68 (27%) children were receiving supplemental oxygen at the time of sputum induction; 65 via nasal prongs or cannulae and three via headbox oxygen 30 children (12%) were known to be HIV-infected at enrolment; of the children whose HIV status was unknown, 139 had HIV testing of whom 20 tested positive by PCR, and an additional 45 tested positive by ELISA with clinical features of HIV infection, thus, 95 children (38%) were judged to be HIV infected
Intervention	*Nasogastric lavage* 3 specimens Early morning gastric lavage after an overnight fast of at least 4 hours The first lavage was done the day after enrolment, and 2 more were taken on consecutive mornings

Bibliographic reference	**Zar HJ, Hanslo D, Apolles P, Swingler G and Hussey G (2005) Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 365(9454): 130-4**
	Lavage was done approximately 18 hours after sputum induction A nasogastric tube was passed before the child got up and gastric contents aspirated If the aspirate was less than 20 ml, 20 ml of normal saline was inserted down the tube, left for 2 to 3 minutes, then aspirated Additional 5 to 10 ml samples of normal saline were inserted and aspirated until a minimum of 20 mL of aspirate was obtained Samples were cultured singly in a BACTEC 12B bottle containing supplemented Middlebrook medium for 6 weeks
Comparator	*Induced sputum* 3 specimens Sputum induction was undertaken after a 2 to 3 hour fast Children were pretreated with 200 µg salbutamol via metered dose inhaler with attached to prevent bronchoconstriction A jet nebuliser that was attached to oxygen at a flow rate of 5 l per minute delivered 5 ml of 5% sterile for 15 minutes; thereafter, chest percussion was done over the anterior and posterior chest wall Sputum was obtained by suctioning through the nasopharynx with a sterile mucus extractor Sputum induction was done on three consecutive days unless children were discharged, were intubated, or died within this time The first specimen was obtained on the day of enrolment; subsequent specimens were obtained on the second and third days after admission, about 6 hours after the early morning gastric lavage Samples were cultured singly in a BACTEC 12B bottle containing supplemented Middlebrook medium for 6 weeks

Bibliographic reference	**Zar HJ, Hanslo D, Apolles P, Swingler G and Hussey G (2005) Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 365(9454): 130-4**
Location	Cape Town, South Africa
Outcomes measures and effect size	Culture positivity – 1st specimen • nasogastric lavage = 19/250 • induced sputum = 37/250 Culture positivity – 3 specimens • nasogastric lavage = 38/250 • induced sputum = 51/250
	Smear positivity – 1st specimen • nasogastric lavage = 8/250 • induced sputum = 19/250 Smear positivity – 3 specimens • nasogastric lavage = 17/250 • induced sputum = 25/250
	Adverse events – reported for sputum induction only No serious adverse reactions attributable to sputum induction occurred during or after the procedure; the most common adverse events were an increase in coughing in 293 procedures (41%), mild epistaxis in 55 (8%), vomiting in three (0·4%), and wheezing that was responsive to an inhaled bronchodilator in two (0·3%) 16 (2%) episodes of transient hypoxia were recorded during sputum induction in which the arterial oxygen saturation dropped below 92%; the lowest oxygen saturation in any child was 88%
Source of funding	Funded by the Medical Research Council, South Africa, and the ICH fund, Red Cross Children's Hospital
Comments	

1.1.22 Zar, 2012

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clinical Infectious Diseases* 55(8): 1088-95**
Study type	*Cross-sectional*

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clinical Infectious Diseases* 55(8): 1088-95**
Study quality	Study limitations Was a consecutive or random sample of patients enrolled? *yes* Was a case-control design avoided? *yes* Did the study avoid inappropriate exclusions? *yes* Participants blinded? *no* Individuals administering care blinded? *unclear* Investigators blinded? *unclear* Appropriate length of follow-up? *yes* Precise definition of outcome? *unclear* Valid and reliable method of outcome measurement? *yes* Was there an appropriate interval between specimen collections? *yes, paired specimens* Inconsistency Groups received the same care apart from the intervention(s) studied? *yes* Equal follow-up? *yes* Groups comparable for availability of data? *yes* Indirectness Population matches population of interest? *yes* Intervention matches intervention of interest? *yes*

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clinical Infectious Diseases* 55(8): 1088-95**
	Outcomes match the outcomes of interest? *yes*
Number of patients	535 had at least one paired induced sputum and nasopharyngeal aspirate
Patient characteristics	*Inclusion* Children under 15 years of age hospitalized with suspected pulmonary tuberculosis The reasons for hospitalisation included severe or very severe pneumonia defined by WHO criteria, the need for oxygen or intravenous therapy, or social conditions precluding home care Children were eligible if they had a cough for more than 14 days and if one of the following conditions existed: a household tuberculosis contact within the preceding 3 months, weight loss or failure to gain weight within the preceding 3 months, a positive skin test to purified protein derivative, or a chest radiograph suggestive of pulmonary tuberculosis *Exclusion* Children who had received tuberculosis drug(s) for longer than 72 hours Children without at least one paired IS/NPA specimen Children with extrapulmonary tuberculosis *Characteristics of included participants*

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clinical Infectious Diseases* 55(8): 1088-95**

	All
Age (months; median and IQR)	19.0 (11.2–38.3)
Male n (%)	294 (55.0)
HIV infection n (%)	117 (21.9)
HIV WHO clinical staging n (%)	
Stage 1	10 (8.6)
Stage 2	35 (29.9)
Stage 3	42 (35.9)
Stage 4	30 (25.6)
HIV CDC immune category n (%)	
None	23 (22.1)
Moderate	35 (33.7)
Severe	46 (44.2)
History of prior tuberculosis N (%)	56 (10.4)
Radiological changes suggestive of TB n (%)	333 (67.4)
Commenced on anti-tuberculosis treatment n (%)	283 (52.9)
Z scores (median and IQR)	
HAZ	– 1·4 (– 2·5 to – 0·4)
WAZ	– 1·4 (– 2·3 to – 0·5)
WHZ	– 0·59 (– 1·5–0·3)
Malnutrition (WAZ score < – 2) n (%)	68 (15.6)
Tuberculin skin-positive n (%)	191 (39.2)

Intervention	*Nasopharyngeal aspiration* Sample obtained before the induced sputum specimen Two drops of sterile saline were instilled into each nostril and the nasopharynx was suctioned using a sterile catheter with a mucus trap

Bibliographic reference	**Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W and Nicol MP (2012) Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clinical Infectious Diseases* 55(8): 1088-95**
	Specimens were examined using the Xpert MTB/RIF assay and cultured for 6 weeks using the BACTEC MGIT 960 system
Comparator	*Induced sputum* Sputum induction was done at least 30 minutes after a nasopharyngeal aspiration, following a 2–3 hour fast Specimens were examined using the Xpert MTB/RIF assay and cultured for 6 weeks using the BACTEC MGIT 960 system
Location	Cape Town, South Africa
Outcomes measures and effect size	Culture positivity • nasopharyngeal aspiration = 61/535 • induced sputum = 84/535
	Xpert positivity • nasopharyngeal aspiration = 57/535 • induced sputum = 69/535
Source of funding	Supported by the National Institutes of Health, USA, the National Health Laboratory Services Research Trust, the Medical Research Council of South Africa, and The Wellcome Trust
Comments	