The efficacy of prophylactic antibiotics in the management of pneumonitis following kerosene (paraffin) ingestion in children

KATE HELENE BALME
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Supervisors:

Professor Heather Zar, Department of Paediatrics and Child Health, University of Cape Town

Professor Michael Mann, Department of Paediatrics and Child Health, University of Cape Town

DECLARATION

I, *KATE HELENE BALME*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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LIST OF ABBREVIATIONS

bpm = breaths per minute

BTS = British Thoracic Society

CAP = community acquired pneumonia

CPAP = continuous positive airway pressure

CRF = case report form

CXR = chest X-ray

HAART = highly active antiretroviral treatment

HIV = human immunodeficiency virus

IMCI = Integrated Management of Childhood Illness

IQR = interquartile range

MDI = metered-dose inhaler

PI = principal investigator

PIC = Poisons Information Centre

RCT = randomised controlled trial

RCWMCH = Red Cross War Memorial Children's Hospital

RR = respiratory rate

TB = M*ycobacterium tuberculosis*

URTI = upper respiratory tract infection

WCC = white cell count

WHO = World Health Organisation

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ABSTRACT

CONTEXT

Hydrocarbons, especially kerosene (paraffin), are the most common agents involved in childhood poisoning in developing countries. In South Africa, there are an estimated 40 000 to 60 000 kerosene ingestion cases per year. At Red Cross War Memorial Children's Hospital (RCWMCH), the number of cases may be decreasing with an average of 100 cases per annum between 2003 and 2008 and fewer than 100 hundred cases per annum from 2009 to 2011. The lung is the target organ affected during kerosene ingestion and aspiration causes a chemical pneumonitis. The resultant inflammatory reaction may make the lungs susceptible to secondary bacterial infection. However, the clinical features of inflammation and infection are difficult to distinguish. A South African study in children concluded that secondary infection is rare, as all recovered spontaneously without antibiotics. There has only been one human study to date which has looked at the role of antibiotics in the management and outcome of children with kerosene-associated pneumonitis.

OBJECTIVES

To assess the efficacy of prophylactic antibiotics in the management of kerosene-associated pneumonitis in children; to identify risk factors that may impact on severity and outcome; and to identify common conditions which result in symptoms and signs indistinguishable from kerosene pneumonitis.

METHODS

A double-blind placebo-controlled trial of prophylactic antibiotics in the management of kerosene-associated pneumonitis following ingestion was performed at RCWMCH from July 2010 to September 2011. Sequential children were randomised to receive placebo or amoxicillin. Each child was followed-up at Day 3 and Day 5 post-ingestion. The primary outcome measure was the number of treatment failures in each group, defined as any child who was deteriorating within this time, necessitating a change in treatment regimen. Secondary outcome measures were the length of hospital stay and symptoms and signs at follow-up.

RESULTS

Seventy-four patients were enrolled. Thirty-five (47%) received placebo and 39 (53%) active treatment. In the placebo group, there were 32 treatment successes (32/35, 91%; 95% CI, 78

to 97) and three treatment failures (3/35, 9%; 95% CI, 3 to 22). In the active group, there were 37 treatment successes (37/39, 95%; 95% CI, 83 to 99) and two treatment failures (2/39, 5%; 95% CI, 1 to 17). There was no significant difference between groups in treatment failures (relative risk (RR), 0.60; 95% CI, 0.11 to 3.37). The median length of hospital stay for placebo (0.5 days; IQR, 0 to 1.0) and active (0.5 days; IQR, 0.5 to 1.0) groups was identical. The symptoms and signs at Days 3 and 5 post-ingestion were similar. There were no risk factors for clinical severity at presentation. The only significant risk factor for treatment failure was residence in formal housing (Fischer, $P < 0.05$). Upper respiratory tract infection (URTI) and active *Mycobacterium tuberculosis* (TB) disease, confounding conditions for treatment failure, were found equally in both treatment success and failure groups.

CONCLUSION

Secondary infection of kerosene-associated pneumonitis following ingestion in children is rare. This study supports the view that prophylactic antibiotics do not improve the outcome in children with mild to moderate respiratory illness after kerosene ingestion, but the observations need to be confirmed in a large sample. As there is no evidence to support the use of prophylactic antibiotics and no predictive risk factors for deterioration, routine reassessment of children within 3 days post-ingestion is advised.

Chapter One

BACKGROUND AND LITERATURE REVIEW

Poisoning is one of the five most important causes of unintentional injury deaths in children, behind road traffic injuries, drowning, falls and fire-related burns, as reported in The 2008 World Health Organisation (WHO)/UNICEF 'World report on child injury prevention' (1). Poisoning accounts for 4% of injury deaths under 17 years and 11% of all unintentional injuries in children below 15 years.

In industrialised countries the most frequently ingested substances are household cleaning products, cosmetics, analgesics and cough and cold medications, whereas in developing countries poisoning is more commonly due to ingestion of hydrocarbons, household cleaning products, medications, pesticides and traditional medicines as well as exposure to poisonous plants and animal and insect bites (2). Regional hospital studies from developing countries record the hydrocarbon kerosene (synonymous with paraffin in South Africa) as the leading cause of acute childhood poisoning. In India kerosene poisoning is responsible for 46 to 60% of childhood poisoning (3, 4, 5, 6), in Sri Lanka 47% (7), in Pakistan 29 to 50% (8, 9), in South Africa 16 to 78% (10, 11, 12, 13), in Kenya 62% (14), in Botswana 47% (15) and in Zimbabwe 12 to 20% (16, 17).

Accurate national data on morbidity and mortality associated with kerosene poisonings in developing countries are not readily available, as surveillance systems are inadequate (18). In South Africa, figures are mostly derived from the number of patients with kerosene ingestion presenting to hospitals. However, this method grossly underestimates the incidence as many incidents occur in rural areas where patients are unable to access health care facilities, mild cases are not taken to hospital, cases may be missed if recorded by their final diagnosis and not initial cause of injury, and fatalities are often not recorded as unnatural deaths. The authors (18) estimated the incidence of childhood kerosene ingestion between 40 000 and 60 000 cases annually in South Africa. At Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town South Africa, for each of the six years (2003 to 2008), kerosene ingestion presentations were on average 100 patients per annum and constituted over 20% of all poisoning cases seen (19). From 2009 until the start of the study in July 2010, there were a further 144 incidents of kerosene ingestion (unpublished data from the RCWMCH Poisons Information Centre (PIC) Clinical Poisonings Database).

The lung is the target organ affected during ingestion of kerosene (20, 21, 22). Aspiration results in a chemical pneumonitis. Management consists of supportive therapy focusing on oxygenation and ventilation. Most children recover completely (13, 23).

Respiratory symptoms and signs are the main clinical features after ingestion. Immediate gasping, choking or cyanosis following ingestion is likely due to inhalation of vapours displacing oxygen in the alveoli (13, 20, 22, 24, 25). If persistent, these symptoms indicate aspiration (20, 21, 22, 25). The USA Co-operative Kerosene Poisoning Study in the late 1950s (26) aimed to evaluate gastric lavage and other factors in the treatment of accidental ingestion of petroleum distillates in children. In patients who ingested kerosene and were not treated with gastric lavage, 53% developed pulmonary complications including pneumonitis. In further hospital studies, 54 to 90% of patients developed respiratory symptoms and signs (10, 23, 27, 28, 29). These figures are based on children presenting to hospital and therefore probably overestimate the number of patients who develop respiratory complications after kerosene ingestion.

Animal studies show that pneumonitis results from aspiration, not gastrointestinal absorption (24, 30, 31). Aspiration occurs either during initial ingestion or subsequent vomiting. Low viscosity, low surface tension, high volatility and poor water solubility increase the risk of aspiration and determine toxicity (20, 21, 22, 24, 25). Pulmonary damage is likely due to chemical destruction of surfactant in the alveoli and distal airways (22, 24) as well as the lipophilic hydrocarbons extending across the interstitial space to render the vascular endothelium more permeable (20, 22). The subsequent pneumonitis is a haemorrhagic alveolitis and vasculitis with atelectasis, pulmonary oedema and bronchospasm causing ventilation-perfusion mismatching and hypoxia (20, 24).

There is an important conceptual difference between aspiration pneumonitis and aspiration pneumonia. Aspiration pneumonitis is a chemical injury after inhalation of regurgitated sterile gastric contents whereas aspiration pneumonia occurs after inhalation of oropharyngeal secretions containing predominantly anaerobic organisms (32). This difference impacts on the likelihood of infection after aspiration and the potential need for therapeutic antimicrobials. Kerosene pneumonitis is aligned with the former mechanism of injury and therefore early infection is theoretically rare. However, chemical irritation does render lung tissue more susceptible to superimposed bacterial infection. A possible mechanism for this in animal models is disruption of the alveolar surface, leading to altered bacterial clearance and subsequent overgrowth (24, 33).

Both chemical pneumonitis and secondary bacterial infection provoke an inflammatory response. In animals, the natural course of kerosene pneumonitis is an acute alveolitis which

peaks at 3 days and resolves by 10 days, followed by a process of alveolar proliferation and thickening which peaks at 10 days and resolves by 2 weeks (20, 21, 22, 24, 34).

Animal studies have investigated both bacterial superinfection and antibiotic use. In one study (34), intratracheal instillation of either kerosene or saline to baboons negated the possibility of oral bacterial contamination. Histological samples confirmed established kerosene pneumonitis in the experimental group, but no visible organisms or positive lung cultures in either the experimental group or controls, highlighting that secondary bacterial infection is rare. In another study (33) in guinea pigs, a control group given nothing was compared to experimental groups given intragastric kerosene and differing treatments. Lung cultures showed no difference in recovery rates of organisms in controls and those given kerosene. This supports the view that kerosene ingestion does not increase the risk of bacterial infection. The experimental group was further used to assess the impact of antibiotic treatment on kerosene pneumonitis by comparing those given no treatment, procaine penicillin, ampicillin or cephalothin. There were no differences in positive culture rates between experimental subgroups, supporting the view that there is no benefit in prophylactic antibiotics. In one further study (35), dogs given intratracheal median lethal doses of kerosene received either dexamethasone and ampicillin or nothing. There were no significant differences in mortality or in clinical, radiological and pathological findings, demonstrating no benefit in early antibiotic therapy and the use of steroids.

Both inflammation and infection clinically manifest as tachypnoea, hypoxia, fever and a raised white cell count. Therefore it is difficult to distinguish clinically between the two. Fever persisting beyond 48 hours may suggest bacterial superinfection (20, 21, 22), but many authors suggest that bacterial infection is actually rare (13, 23, 24). The dilemma comes in knowing when to initiate antibiotic therapy.

A study on children (n = 111) admitted to a rural South African hospital investigated the epidemiological, clinical and radiological manifestations of kerosene ingestion (23). In addition, the development, diagnosis and natural course of secondary infection with kerosene-associated pneumonitis was investigated. No prophylactic antibiotics were prescribed, but therapeutic antibiotics could be given at the discretion of the treating doctor. The day of ingestion was Day 0 (n = 104); patients admitted later (n = 7) were still eligible for inclusion and placed in the appropriate day category. Each child had a chest X-ray (CXR) on admission and a white cell count (WCC) done within 24 hours of admission. Fever and respiratory distress on Day 1 were taken as suspicious of secondary bacterial infection, at which time a blood culture and CXR were done. If fever and respiratory distress were present at Day 4, nosocomial infection was considered a possibility and a CXR, WCC and

blood culture were repeated. Patients were discharged once respiratory distress and any central nervous system manifestations had resolved; the disappearance of fever was not required. Fever was defined as any temperature above 37.5 degrees Celsius (˚C). Respiratory distress was present if there was dyspnoea, which was according to grunting or recession and/or tachypnoea (respiratory rate ≥40 breaths per minute (bpm) for infants and ≥30bpm above 1 year).

There was an average hospital stay of 2.6 days. On Day 1, 50% (54 of 109) patients fulfilled criteria for suspected secondary bacterial infection. Only 4% (*n* = 2) of those who had blood cultures performed had a positive culture. The mean WCC of those with suspected secondary infection on Day 1 was significantly greater than those in whom secondary infection was not suspected. On Day 4, 17 patients were considered to have secondary infection; of these, 6% (*n* = 1) had a positive blood culture. The number of children still admitted at Day 4 was not reported. There is also no comment as to how many children were suspected of secondary bacterial infection on both days. Of the total group of patients, only one child was given antibiotics. She presented 7 days post-ingestion with ongoing fevers and respiratory distress. She had pneumatocoeles on CXR and a negative blood culture. None of the patients with positive blood cultures were given therapeutic antibiotics and all followed the typical clinical course of spontaneous resolution following kerosene ingestion.

Reed and Conradie (23) state that although the use of blood cultures to detect secondary bacterial infection has limitations, it appears that secondary bacterial infection is rare. They question the significance of the positive cultures isolates as these children recovered without antibiotic therapy and they also reflect on the inability of a raised WCC to differentiate between secondary infection and the inflammatory reaction to kerosene ingestion. Some weaknesses were evident in the study's design. The use of parameters such as fever and respiratory distress at Day 1 may have overestimated the number of patients with suspected secondary infection, as these features could merely have reflected the ongoing inflammatory response to a chemical pneumonitis. The values for age-specific tachypnoea were also on the lower end of the range and therefore more children may have been assessed as having a raised respiratory rate. However, it is difficult to dispute the conclusions that most children recover with antipyretics and oxygen therapy only, and that secondary infection is rare.

To date, there is only one human trial in children (*n* = 100), which analysed the efficacy of antibiotics after kerosene ingestion (36). However, this study has major methodological limitations. Patients were drawn from cases admitted following accidental kerosene ingestion, with no further inclusion criteria defined. There were 20 subjects in each of four treatment groups: Group A (ampicillin and metronidazole), Group B (carbenicillin), Group C

(ampicillin) and Group D (metronidazole). The response to treatment was defined as clinical resolution of fever, tachypnoea and chest rales and improvement in the grading of X-ray changes. Fever and tachypnoea were not defined. A fifth group of 20 subjects, which the authors termed a control group, received no antibiotics for 48 hours. If they remained asymptomatic or improved in symptoms during this observation period, they continued without antibiotics. If they remained symptomatic or developed symptoms they were given antibiotics as per Group A. There was no definition for the term "symptomatic".

The time to clinical recovery for the four treatment groups was between 5 and 7 days. Although Group A seemed to recover slightly quicker, there was no statistically significant difference between the four treatment groups. In the control group, nine of the 20 children were symptomatic at 48 hours and given antibiotics; all nine remained symptomatic on Day 8. There is no comparison of the time to recovery between treatment and control groups. Radiological abnormalities were found in 98 (98%) of all cases; 32 had no "physical signs in the chest". The numbers of patients with radiological deterioration at Day 8 for Groups A to D were two (10%), three (15%), three (15%) and seven (35%), respectively. The control group had seven (35%) cases with radiological deterioration at Day 8, all of whom were also symptomatic and received antibiotics.

The authors suggest some benefit with prophylactic antibiotics with both aerobic and anaerobic cover, but they suggest that further studies are needed. They acknowledge the limitations of their control group, but for the control patients who did receive an antibiotic after the 48-hour observation period, they suggest an unsatisfactory response to delayed initiation of antibiotic treatment in symptomatic patients.

There are several methodological limitations to this study. The lack of clear inclusion criteria may have led to the enrolment of patients without respiratory symptoms or signs, resulting in a bias towards a successful treatment response. The number of subjects was small. The methods for assessing response to treatment were unclear as clinical signs were poorly defined. The study required that clinical features should have resolved to indicate improvement. If the natural course of pneumonitis in children is similar to that in animals, the authors expected resolution within a period of time less than the natural history of the illness. Those with improving yet still-present signs and possibly even those with static signs may have been incorrectly deemed to be non-responders and mostly likely resulted in an overestimate of delayed responders. In addition, a satisfactory response to treatment required clinical and radiological improvement. However, the correlation between clinical signs and radiological changes is poor (20, 21, 22, 25), as demonstrated by Singh et al. Eade et al (24) state that 75% of patients with kerosene ingestion will have radiographic evidence of lung

involvement, of whom only 25 to 50% develop respiratory symptoms and signs. Conversely, some children with clinical signs will have a normal CXR. Singh et al admit to an inadequate control group as almost 50% within the control sample received an antibiotic during the course of the study and therefore the time to recovery could not be compared to the treatment groups to assess the impact of antibiotic therapy. The assessment criteria for remaining off antibiotics also appear to differ from those used in assessing treatment response, as a true control was either asymptomatic or improving in symptoms whereas evidence of treatment response required resolution of clinical findings. Lastly, bearing in mind the aforementioned sterile nature of kerosene-associated pneumonitis (32), Singh et al inappropriately based the choice of antibiotic on the premise that aspiration pneumonia requires anaerobic cover. This study shows the treatment response to different classes of antibiotics, but does not show if an antibiotic is needed.

Using the total number of study patients (*n* = 111) from Reed and Conradie (23), the number with suspected infection decreased from 54 (49%) on Day 1 to 17 (15%) on Day 4, without antibiotic intervention. The number of positive blood cultures halved. Singh et al's (36) control group had 45% (9 of 20) with suspected secondary infection after 48 hours. They were given antibiotic therapy and remained symptomatic at Day 8. These studies cast doubt on the efficacy of prophylactic antibiotics in the management of kerosene-associated pneumonitis. As there is currently no agreement on the benefit of prophylactic antibiotics, there is wide variability in practice globally. In South Africa, although some studies state that secondary infection in children after kerosene ingestion is rare and routine prophylactic antibiotics are unnecessary (13, 23), another reports the use of prophylactic antibiotics as common practice (37). A possible justification for this is the large burden of malnutrition, human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (TB) disease which places immunocompromised children potentially more at risk of superinfection and clinicians are nervous to withhold antibiotics. In the past, the policy at RCWMCH was to give all patients with suspected pneumonitis following kerosene ingestion prophylactic antibiotics but, because of lack of evidence, this was changed and the decision is currently left to the discretion of the treating doctor.

As the data is limited, it is clear that further investigation is required to determine the efficacy of prophylactic antibiotics in children after kerosene ingestion. Using the figures from the studies of Reed and Conradie (23) and Singh et al (36), the suspected secondary infection rate at 48 to 96 hours for patients not receiving prophylactic antibiotics was 15 to 50%. It is reasonable to assume that these children should be considered for an alteration in their management. This would mean either introducing an antibiotic for those previously without or broadening the antimicrobial cover for those already receiving treatment.

The unsubstantiated practice of prescribing prophylactic antibiotics may lead to the unnecessary use of resources in developing countries. Even worse, it may contribute to the development of antibiotic-resistant organisms. Given the lack of strong evidence and of randomised controlled trials (RCT), we aimed to investigate the efficacy of prophylactic antibiotics in children with accidental kerosene ingestion.

METHODS

A double-blind placebo-controlled trial of prophylactic antibiotics in the management of kerosene-associated pneumonitis following ingestion was performed, according to the study protocol (Appendix A). Sequential children attending Red Cross War Memorial Children's Hospital (RCWMCH) from 21 July 2010 until 21 September 2011 with known or suspected kerosene ingestion were randomised to receive either placebo or amoxicillin.

Primary objective

The primary objective was to assess if prophylactic antibiotics affect the clinical course of kerosene-associated pneumonitis in children. The primary outcome measure was the number of treatment failures in the placebo and active groups. A treatment failure was a patient who at any time deteriorated necessitating a change to the treatment regimen. Secondary outcome measures were the length of hospital stay for medical reasons and symptoms and signs at Day 3 and Day 5 post-ingestion.

Secondary objectives

The secondary objectives were to identify risk factors that may impact on the severity and outcome of pneumonitis following kerosene ingestion and to identify common conditions which result in symptoms and/or signs indistinguishable from kerosene pneumonitis. The presence of these factors or conditions may warrant early use of prophylactic antibiotics.

Setting

The study was done in the Medical Emergency Department at RCWMCH in Cape Town South Africa. RCWMCH is a 288-bed public teaching hospital with tertiary and regional functions, serving children under the age of 13 years. It is a referral hospital with 24-hour trauma and emergency units, both of which have overnight inpatient beds. Referrals are from clinics and day hospitals in the Cape Town metropole and regional hospitals in the Western Cape Province. In 2007, the paediatric population (0 to 14 years) of the metropole was 901 385 and of the Province 1 3877 800 (38). The study was temporarily suspended during the PI's annual leave (30 September to 1 October 2010, 1 to 12 November 2010, 28 to 29 April 2011 and 15 to 16 September 2011).

Sample size calculation

The average of 100 children per annum attending RCWMCH with the diagnosis of kerosene ingestion would give a sample of 200 children over a two-year period, with 100 patients in

each group. From the postulated secondary infection rate of 15 to 50% for children not receiving an antibiotic we took a midway point of 25% as the estimate of the treatment failure rate in the placebo group. With no information available on the treatment failure rate in the active group, we arbitrarily took failure rates of 10% and 5%. With 25% and 5% treatment failure rates for placebo and active groups respectively, at a level of significance of $\alpha = 0.05$ a sample size of 100 per group gives a power of 0.98 and with failure rates of 25% and 10% a power of 0.80.

Participants

Children older than 3 months with respiratory symptoms or signs after suspected or known kerosene ingestion were eligible for inclusion (Table 1). Symptoms were reported by the caregivers and signs were documented in the patient's referral letter or witnessed by the on-duty doctor at RCWMCH. Written informed consent, available in any of three official languages (English, Afrikaans and Xhosa, Appendices B1 to 3), was obtained from the parent or legal guardian. A translator was used where necessary.

Exclusion criteria included severe illness requiring antibiotics and allergy to amoxicillin (Table 1).

Table 1: Inclusion and exclusion criteria for study participation

INCLUSION CRITERIA • Kerosene ingestion within the preceding 24 hours • Older than 3 months • Respiratory symptoms (history of cough or difficulty in breathing) AND/OR • Respiratory signs (age-specific tachypnoea*, chest indrawing, stridor, wheeze) • Informed consent obtained from parent or legal guardian • Resident in the RCWMCH drainage area and able to come for two follow-up visits *Age-specific tachypnoea regarded as: Respiratory rate > 50 breaths per minute (3 to 12 months) or Respiratory rate > 40 breaths per minute (12 months to 5 years)
EXCLUSION CRITERIA • Asymptomatic and no clinical signs • Too ill to be excluded from receiving an antibiotic as judged by: o Requiring more than 2L/min nasal-prong oxygen o Requiring continuous or intermittent positive airway pressure ventilation o Fever > 40˚C • Needing an antibiotic for another reason e.g. otitis media, tonsillitis • Current antibiotic use, prior to kerosene ingestion • Allergic to amoxicillin

Recruitment occurred 24 hours a day, 7 days a week. As there was only one principal investigator (PI), the study was set up to facilitate maximal recruitment at all times irrespective of the PI's presence in the Medical Emergency Department. During working hours, the PI was contacted directly by the on-duty triage nurses when a potential patient attended. For after-hours presentation, the on-duty medical officers were trained to perform basic enrolment of eligible children, which involved an explanation of the study, obtaining informed consent and preparation and prescribing of the study drug. A study box was kept in the medical emergency room containing a list of inclusion and exclusion criteria, instructions for enrolment, numbered study drug bottles, specific prescription charts and an admission questionnaire (Appendix C) for standardised recording of clinical findings. The PI was available via telephone for any questions from the parent or enrolling medical officer. Each morning, the PI would contact the admissions ward to find out if there were any new inpatients. A new recruit would then be seen by the PI before discharge to complete any missing information, confirm contact details, ensure caregiver study understanding, give follow-up appointments and check the correct dose of study drug was prescribed. After-hours ambulatory patients were discussed with the PI before going home, to ensure the same standard of care.

Study drug

The study drug was an oral preparation prepared by the RCWMCH pharmacy in identical matching glass bottles with identical study drug labels. Amoxicillin powder from 100 bottles of the same manufacturer was decanted into the study drug glass bottles. Glucose powder served as placebo. Both active and placebo study drug required sterile water for mixing. To ensure that the placebo and active were identical, glycerol was added to the placebo's sterile water, to match the consistency of the amoxicillin mixture. The water bottles were opaque and specifically assigned to each study drug bottle. Study drug bottles were prepared in batches of six to ten at a time, depending on the speed of recruitment. In each batch, there was an even number of active and placebo study drug, randomly assigned by the RCWMCH pharmacy. Bottles were numbered and water bottles matched accordingly. The prepared study drug was stored in the hospital pharmacy, except for a few bottles which were kept in the aforementioned study box in the medical emergency room for after-hours enrolment. A study file was kept locked in the RCWMCH pharmacy, containing the study drug preparation recipe and codes. Investigators (other than the pharmacist) were therefore blinded to the treatment regimen.

Participants were assigned study drug in sequential numerical order. The enrolling doctor mixed the study drug and prescribed the dose, all according to clear instructions in the study box. The dose was 20 to 30milligrams per kilogram orally per dose 8 hourly for 5 days. Prior to commencement of the study, doctors and nurses were shown the study drug bottle to avoid confusion or dispensing errors. Patients who were observed as ambulatory patients were given their study drug before going home. Patients who required admission to the short-stay ward for overnight observation received their study drug in the ward and on discharge. For admissions, a bright green sticker indicated the study drug on the prescription chart. All patients were given 5 days of treatment. Study drug adherence was checked by asking the parents to bring the bottle to their follow-up visits (observation) and/or by asking them how much they were giving (history).

Enrolment and measurements

Patients enrolled in the study were managed as per protocols used in the Emergency Unit. Ambulatory patients were observed for a period of 6 to 8 hours post-ingestion and considered for discharge if they remained stable, provided there was a reliable caregiver at home who was aware of possible danger signs and could return to hospital if necessary. This decision was made at the discretion of the treating doctor. Additional medical or social concerns were attended to as required. Each caregiver was given safety advice to avoid further such incidents occurring in the home.

Enrolment measurements were recorded on an admission questionnaire (Appendix C) kept in the patient's hospital folder to standardise the collection of data and to prevent the need for duplication of patient case notes. Measurements included: clinical signs, the presence or absence of possible confounding conditions and risk factors, the results of any investigations performed and the length of hospital stay for medical reasons (number of days). Clinical signs included a detailed recording of respiratory signs as well as other features common to kerosene poisoning, particularly temperature and alteration in mental status. Auricular temperature was recorded using the Braun Thermo Scan, Welch Allyn, USA. Oxygen saturation was measured by the Life Scope bedside monitor (OPV 1500K), Nihon Kohden Corporation, Tokyo, Japan. Hypoxia was defined as a reading of less than 94% in room air (39) and oxygen was then given. A chest X-ray (CXR) was done more than 6 hours post-ingestion at RCWMCH, allowing time for possible radiographic findings to develop. In instances where the CXR had been done before this time period at the referral centres, the CXR was not repeated. Anteroposterior and lateral views were done in all instances. A radiologist at RCWMCH reported on CXR's from both the referral centres and study site. Blood tests were done at the discretion of the admitting doctor. All information was later transcribed to a case report form (CRF) (Appendix D1).

Follow-up and outcome measures

Follow-up was done at 3 and 5 days post-ingestion at RCWMCH, which included weekend appointments if necessary. Patients were asked to present to the hospital's emergency unit at any time before their scheduled appointment if their child showed any signs of deterioration, such as increasing shortness of breath. An appointment card was given to the caregiver so that triage nurses or ward clerks were aware of their reason for return and could notify the PI of their attendance. Transport money was given at the follow-up appointment, in order to avoid the possibility of bias by incentivising attendance.

At follow-up, patients were seen by the PI or occasionally by a medical officer experienced in managing children with common paediatric respiratory illnesses and making decisions regarding the need for readmission or continued home care. Caregivers were questioned about ongoing symptoms and patients were examined for clinical signs. Information was recorded on a follow-up CRF (Appendices D2 and 3) with symptoms of cough, wheeze, shortness of breath and fever; they were either absent or were reported according to their change since previous assessment (resolved, improving, static or deteriorating). Clinical signs followed the same pattern as those at presentation. Further information recorded at follow-up included study drug adherence, the need to attend another medical facility prior to the arranged appointment and any additional information.

An assessment was made at each follow-up (or earlier if required) to determine the primary outcome measure of treatment success or failure. Patients who could remain on their study drug were classified as a treatment success. They were improving, stable or had deterioration not requiring a change to their treatment regimen. Patients who were deteriorating necessitating a change to their treatment regimen were classified as a treatment failure. This is consistent with the study's exclusion criteria, which did not allow patients with severe illness to be entered into a randomised-controlled trial with a placebo group.

Once a treatment failure was identified, the study pharmacist was contacted to break the study code and the patient's management adjusted. Children who had been receiving placebo were started on amoxicillin. Those already on amoxicillin were switched to a broad-spectrum antibiotic, either co-amoxiclavulanic acid or cefuroxime. The reported symptoms and clinical signs of treatment failures were included in the analysis up until the point of alteration of their treatment. Although treatment failures had reached the endpoint of the study, they were followed-up by the PI or an appropriate treating clinician to ensure clinical improvement after treatment was changed.

Possible confounding conditions either for treatment failure or persistence of symptoms and signs at follow-up were identified prior to commencement of the study. They were upper respiratory tract infection (URTI) or active *Mycobacterium tuberculosis* (TB) disease. URTI could result in symptoms of cough and fever and clinical findings of fever. Active TB disease could lead to symptoms of ongoing cough, shortness of breath, wheeze and fever and clinical findings of raised RR, crepitations, wheeze or fever. The indications for investigation for active TB disease were a current TB contact, symptoms (weight loss, loss of appetite, failure to thrive, nightsweats) and/or suggestive CXR. Investigation included a Mantoux and gastric washings and/or nasopharyngeal aspirate and/or induced sputum.

Possible risk factors likely to impact on pneumonitis severity or outcome (treatment failure or persistence of symptoms and signs) were post-ingestion vomiting, young age, household smoking contacts, HIV exposure or infection, malnutrition, prior respiratory history and socioeconomic factors such as housing, electricity and parental level of education. The presence or absence of these factors was recorded according to study definitions (see definition of terms). Patient's weight (kilograms) was recorded on a Seca electronic scale. The anthropometric values of weight-for-age were plotted manually by the PI on the new South African Road to Health Charts according to recently updated WHO Child Growth Standards (40). They were reported as normal or abnormal (see definition of terms).

The presence or absence of confounding conditions and risk factors was updated throughout the course of study participation.

Where patients did not return for their scheduled appointments, three attempts were made to contact each patient. If they were contacted by phone, a record of symptoms was taken via telephone interview; however no clinical signs were documented for these patients. If a patient was worse via telephonic assessment, they were asked to attend RCWMCH immediately. If they were unable to be contacted after three attempts, they were recorded as no contact.

Definition of terms

For the purposes of the study, the following definitions applied:

- Kerosene = paraffin
- Age-specific tachypnoea:
    - respiratory rate (RR) > 50 breaths per minute (3 to 12 months)
    - RR > 40 breaths per minute (12 months to 5 years)
- RR severity (3 to 12 months)(41)
    - normal: ≤ 50bpm
    - mild to moderate: 51 to 70bpm
    - severe: ≥ 71bpm
- RR severity (12 months to 5 years)(41):
    - normal: ≤ 40 breaths per minute (bpm)
    - mild to moderate: 41 to 50bpm
    - severe: ≥ 51bpm
- Recessions:
    - mild: intercostal retractions only
    - moderate: intercostal and subcostal retractions
    - severe: intercostal and subcostal retractions and accessory muscle use
- Fever: temperature ≥ 37.5 Celsius (˚C)(42) taken by auricular measurement
- Temperature severity (41):
    - normal: < 37.5˚C
    - mild to moderate: 37.5 to 38.4˚C
    - severe: ≥ 38.5˚C
- Altered mental status: drowsiness (lethargy), irritability (restlessness)(39)

- Upper respiratory tract infection (URTI): rhinitis, otitis media, tonsillitis, pharyngitis (43):
    - preceding: presence of URTI up to a week before kerosene ingestion
    - new-onset: features of a new URTI at follow-up
- Prior respiratory history: perinatal oxygen or ventilation, prior peripheral airway obstruction and/or use of beta-2-agonist, exercise- or URTI-associated wheeze, history of pneumonia or bronchiolitis
- Nutritional status (40, 44):
    - normal: weight-for-age Z-score above -2 standard deviations (SD)
    - underweight: weight-for-age Z-score between -3 and -2 SD
    - acute severe malnutrition: weight-for-age Z-score below -3 SD
- Spring (September to November), summer (December to February), autumn (March to May), winter (June to August)
- Informal housing: shack, wendy-house, bungalow
- Formal housing: brick house, hostel
- Informal sanitation: bucket toilet, portaloo, long drop
- Formal sanitation: flush toilets (personal or communal)
- Educational grades according to South African Department of Education
- Tertiary education: any diploma, degree, higher qualification after completing school
- Treatment failure: a patient who at any time deteriorated necessitating a change to the treatment regimen
- Treatment success: a patient who at any time was improving, stable or had deterioration but not requiring a change to the treatment regimen.

Data analysis

Data were recorded on admission questionnaires and case reports forms (Appendices C, D1 to 3) and entered into Microsoft Excel 2007. This did not include the treatment group (active or placebo).

After 12 months, the PI requested the study be stopped early. Over the next two months, one of the supervisors (MM) performed an interim analysis. As addressed in detail in the discussion, this supported early stopping on grounds of futility, because the number of treatment failures was much lower than anticipated. The PI was unblinded only after the study had stopped and all data other than the treatment group had been entered into the spreadsheet and prepared for analysis.

It was decided that the statistical analysis should be done as originally planned, but the interpretation should highlight the small sample.

Statistical analysis was done using IBM SPSS Version 20 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as *n* (%) and continuous variables as median (interquartile range (IQR)). A *P* value of ≤ 0.05 was considered significant for all situations.

For categorical variables, Fischer's exact test was used for small samples or less frequent occurrences. Chi-Square testing was applied for larger samples or more frequent occurrences. Mann-Whitney or Kruskal-Wallis tests were used for ordinal and continuous variables. Significant correlation between factors and covariates (Spearman's rank coefficient) favoured univariate analysis over binary logistic regression modelling to determine potential risk factors for treatment failure. Continuous variables were categorised for clinical relevance or logistic regression testing.

In some instances, specific clinical parameters or reported symptoms were not recorded or the presence or absence of a risk factor was unknown. The missing values, unknown factors and the flow of patient follow-up account for totals not always adding up to the full number of study participants. In the tables reporting data on clinical presentation, the percentages shown represent the proportion of patients within the groups identified, for example placebo versus active or absent URTI versus preceding URTI. In the tables for Day 3 and Day 5 post-ingestion, the denominator used to calculate proportions for reported symptoms includes those patients who attended and who were telephone interviewed, whereas the denominator for clinical signs is only the patients who attended.

Ethics

Scientific approval was granted by the Departmental Research Committee (SCAH DRC 505/10) and ethics approval by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (FHS HREC 095/2010). Site-specific approval was thereafter gained from the RCWMCH Senior Medical Superintendent. The trial was conducted in accordance with the Declaration of Helsinki 2008 (45). All participant caregivers provided informed consent. The study was registered with clinical trials registries after enrolment of the first patient (ClinicalTrials.gov NCT01253980 and Pan African Clinical Trials Registry PACTR201201000259370).

Chapter Two

RESULTS

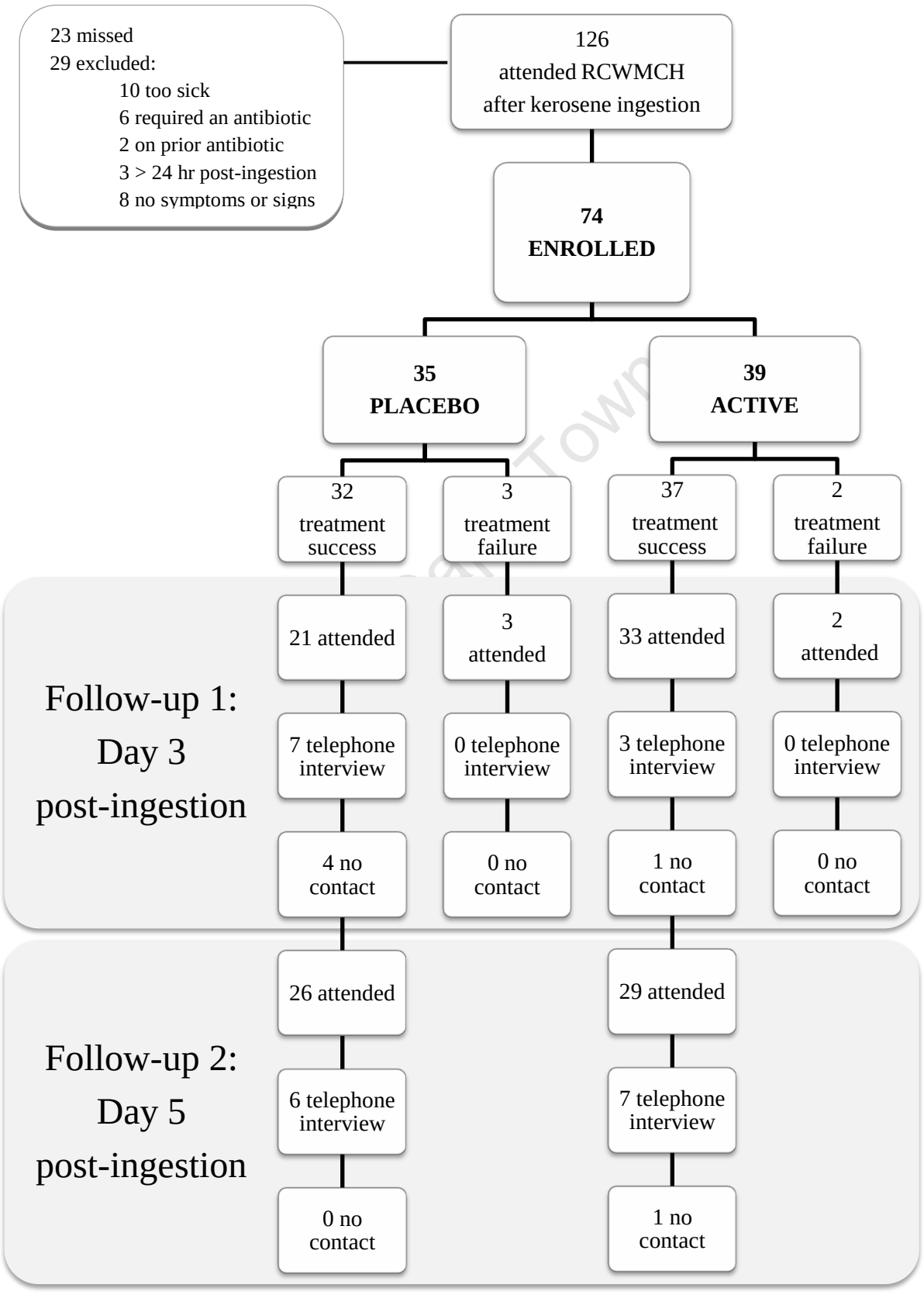
During the 14-month study period, 126 patients attended the outpatient department with the diagnosis of kerosene ingestion of which 74 (59%) were enrolled (Figure 1). Twenty-three patients could not be enrolled as either the PI was on annual leave (six) or the on-duty locum was not aware of the ongoing study. Twenty-nine patients were excluded: 10 were too sick and needed intravenous antibiotics, six needed an antibiotic for another reason, two were on an antibiotic prior to kerosene ingestion, three presented more than 24 hours after ingestion and eight had no symptoms or signs.

Due to the small eventual sample size, decisions had to be made by the PI on whether to include certain patients in the final analysis. Ten patients recruited into the study (four placebo, six active including one treatment failure) had received a single dose of antibiotic at the Day Hospital prior to referral to RCWMCH. Analysis of placebo and active groups excluding these patients (Appendices E1 to 6) came to the same conclusions as when they were included. Another patient who was initially randomised to the placebo treatment arm mistakenly received active antibiotic during his ward admission and on discharge, for which the mother was compliant. The child was continued on antibiotic and placed in the active treatment arm. One further patient with cerebral palsy and included in the active treatment group was improving at 3 days post-ingestion as affirmed by follow-up attendance. Despite reporting being happy with her progress, the mother took her child to the local clinic between 3 and 5 days post-ingestion to have her tonsils reviewed, for which she was given penicillin. The child's progress was satisfactory; she remained in the active treatment arm. The initial protocol defined that patients lost to follow-up would be excluded from the study. However, patients who were not contactable for the first follow-up (n = 5) but were contacted by telephone (n = 4) or attended (n = 1) for the second were not excluded. Only one study patient was not contactable for the second follow-up. At first follow-up, he had an improving reported cough only. He was included in the first follow-up analysis, but excluded from the second by the nature of his missing data. Numerous attempts were made to trace him, which included telephone calls to the patient contact number, telephone calls to the initial referral centre where he was seen on the day of his kerosene ingestion event, and review of the admission register of the neighbouring tertiary hospital within the Cape Town drainage area to which he may have presented if he deteriorated; all proved unsuccessful. One study participant, who was asymptomatic by telephone interview at 3 days post-ingestion, informed the PI of their intent to miss the second appointment, as instructed by the

child's father who felt that he was too well to need any further review. For this patient, the Day 5 follow-up symptoms were all recorded as absent and the signs recorded as per a telephone interviewee.

Of the 74 study participants, there were 21 (28%) ambulatory patients and 53 (72%) admissions. The median length of hospital stay was 0.5 days (IQR, 0 to 1). Only one patient required a brief period of nasal-prong oxygen during overnight admission. Her oxygen saturation was 92%. All other participants had measured saturations above 94% at presentation and follow-up. Therefore, oxygen saturations have only been included in the analysis of clinical presentation for the treatment (placebo versus active) and primary outcome (treatment success versus failure) groups. CXR's were performed on 70 (95%) patients. The CXR was mistakenly omitted in four patients when they were admitted overnight; as they were clinically stable the following day, a routine CXR could not be justified. At follow-up 3 days post-ingestion, 59 (80%) patients attended, 10 (13%) patients were interviewed by telephone and five (7%) patients were unable to be contacted (Figure 1). At second follow-up, 55 patients (80%) attended, 13 (19%) were interviewed by telephone and one (1%) patient was unable to be contacted. The five treatment failures were excluded from the analysis of Day 5 findings.

Figure 1: The flow of study participants through enrolment and follow-up



Baseline characteristics of placebo and active treatment groups

Thirty-five patients (47%) were assigned to placebo and 39 (53%) to active treatment. The groups were similar with regards to demographics, age and gender (Table 2). There were no infants enrolled in the study; the majority (58/74, 78%) were under 24 months (Table 2). The median age of the placebo group, 19 months (IQR, 15 to 21), was similar to the treatment group, median age 20 months (IQR, 16 to 24).

Table 2: Baseline characteristics and event details in placebo and active groups

	PLACEBO ***n*** **= 35**	**ACTIVE** ***n*** **= 39**	***P*-value**
PATIENT MEASUREMENTS			
Male:female, *n* (%)	21:14 (60:40)	24:15 (62:38)	>0.05
Age (months)*	19 (15-21)	20 (16-24)	>0.05
Weight (kg)*	11.8 (10.0-12.4)	11.3 (10.1-12.9)	>0.05
INGESTION EVENT, *n* (%)			
Hours post-ingestion at enrolment*	6.0 (3.5-11.0)	6.0 (4.0-8.0)	>0.05
Season			>0.05
Spring	8 (23)	10 (26)	
Summer	10 (29)	11 (28)	
Autumn	5 (14)	6 (15)	
Winter	12 (34)	12 (31)	
Witnessed	13 (37)	11 (28)	>0.05
Occurred at home	19 (54)	27 (69)	>0.05
Container			>0.05
Paraffin bottle	8 (23)	12 (31)	
Juice bottle	20 (57)	22 (56)	
Other (paraffin lamp)	2 (6)	1 (3)	
Given milk and/or water at place of ingestion	24 (69)	28 (72)	>0.05

*Values are median (interquartile range)

Most children (63/73, 85%) came from five peri-urban suburbs, Khayelitsha, Nyanga, Philippi, Gugulethu and Mitchell's Plain (placebo *n* = 29, 83%; active *n* = 34, 87%). Few patients resided in formal housing in placebo (*n* = 13, 37%) and active (*n* = 10, 26%) groups. Electricity was available in the home in placebo (*n* = 26, 74%) and active (*n* = 25, 64%) groups respectively. Most cases occurred in winter, followed by summer, spring and autumn (Table 2).

Children presenting to the Emergency Department were either referred by primary health care centres (68 patients; 31 placebo, 37 active) or presented directly to RCWMCH (six patients; four placebo, two active). Patients in the placebo group were seen within a median time of 6.0 hours (IQR, 3.5 to 11.0) post-ingestion (Table 2) and those in the active group, median 6.0 hours (IQR, 4.0 to 8.0). The ingestion event (Table 2) was mostly unwitnessed (placebo *n* = 22, 63%; active *n* = 26, 67%) and occurred in the home (placebo *n* = 19, 54%; active *n* = 27, 69%). In over half of all events (*n* = 42, 57%), kerosene had been decanted into a juice bottle for storage. Most children (*n* = 52, 74%) were given milk and/or water after ingestion at the place of the incident.

The placebo and active groups had similar pneumonitis severity at presentation (Table 3).

Table 3: Clinical findings in placebo and active groups at presentation

	PLACEBO ***n* = 35**	**ACTIVE** ***n* = 39**	***P* value**
INCLUSION CRITERIA, *n* (%)			
Symptoms only	6 (17)	7 (18)	>0.05
Signs only	2 (6)	1 (3)	>0.05
Symptoms and signs	27 (77)	31 (79)	>0.05
SYMPTOMS, *n* (%)			
History of coughing	33 (94)	38 (97)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	48 (40–56)	44 (33-58)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	11 (31)	10 (26)	
Severe (> 50bpm)	10 (29)	12 (31)	
Recessions			>0.05
Mild	8 (23)	8 (21)	
Moderate	1 (3)	3 (8)	
Flaring	11 (31)	13 (33)	>0.05
Grunting	6 (17)	6 (15)	>0.05
Wheeze	2 (6)	5 (13)	>0.05
Crepitations			>0.05
Localised	4 (11)	5 (13)	
Diffuse	6 (17)	6 (15)	
Oximetry (%saturation)*	99 (97-99)	98 (97-99)	>0.05
Temperature (˚C)*	37.2 (36.7-38.3)	37.2 (36.7-38.3)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	6 (17)	9 (23)	
Severe (> 38.5˚C)	8 (23)	7 (18)	
Altered mental status	8 (23)	11 (28)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

The presence or absence of possible confounding conditions or risk factors was similar between groups (Table 4).

Table 4: Possible confounding conditions and risk factors in placebo and active groups

	PLACEBO ***n*** **= 35**	**ACTIVE** ***n*** **= 39**	***P*** **value**
POSSIBLE CONFOUNDING CONDITIONS**,** *n* (%)			
Upper respiratory tract infection (URTI)			>0.05
Preceding	9 (26)	8 (21)	
New-onset	15 (43)	16 (41)	
Active TB disease	2 (6)	1 (3)	>0.05
POSSIBLE RISK FACTORS**,** *n* (%)			
Vomiting post-ingestion	19 (54)	22 (56)	>0.05
Age categories (months)			>0.05
12-23	29 (83)	29 (74)	
24-35	5 (14)	8 (21)	
> 36	1 (3)	2 (5)	
Smoking contact	14 (40)	12 (31)	>0.05
HIV exposed*	13 (37)	7 (18)	>0.05
Prior respiratory history	7 (20)	10 (26)	>0.05
Formal housing	13 (37)	10 (26)	>0.05
Electricity	26 (74)	25 (64)	>0.05
Educational status (mother)			>0.05
< 10 years formal education	8 (23)	10 (26)	
> 10 years formal education	20 (57)	25 (64)	
Tertiary	7 (20)	4 (10)	

*As there was only 1 HIV-infected child (placebo), she was included in the analysis according to HIV-exposure status (exposed versus unexposed)

Clinical course from presentation to Day 3 post-ingestion

There were 53 patients, 27 placebo and 26 active, who either improved or remained stable between presentation and Day 3 post-ingestion. These patients therefore met the criteria for classification as a treatment success.

A further 14 patients, five placebo and nine active, were well but had one or two deteriorating or new-onset clinical signs at Day 3 post-ingestion. Two children (one placebo, one active) had an increase in respiratory rate (RR) of 8bpm from presentation to Day 3 post-ingestion, one being a child with hypotonic cerebral palsy with many respiratory secretions. One patient (placebo) developed mild recession at Day 3 post-ingestion. Two patients (one placebo, one active) had both new-onset wheeze and crepitations; one responded to an inhaled beta-2-agonist. A third patient (placebo) had new-onset wheeze only. Four patients (all active) had new crepitations on Day 3 post-ingestion, one patient also showing irritability. Another patient (placebo) had new fever and irritability and three patients (3 active) new-onset irritability.

Two children had signs of deterioration at Day 3 post-ingestion due to new-onset URTI. One patient (active), who was febrile at presentation, had an increase in temperature and developed irritability, but maintained a normal-for-age RR. The other patient (active) had a new-onset fever and there was a large rise in RR by 19bpm.

None of the aforementioned 16 patients had a clinical indication for a repeat CXR. All 16 were well with one or two new-onset clinical signs or had an identifiable reason for deterioration which did not require a change to their treatment regimen. They therefore met the criteria for classification as a treatment success.

The remaining 5 patients (three placebo, two active) had signs of deterioration within 3 days post-ingestion, to such an extent that they required a change to their treatment regimen. They were therefore treatment failures. A description of these patients is given below, detailing the major symptoms and signs contributing to the decision that a change in treatment was essential (Tables 5A and B and accompanying text).

Four of the five treatment failures had a rise in RR of 12-17bpm from presentation (Table 5B); all into the abnormal-for-age range. Three of the four treatment failures with tachypnoea developed grunting, the only children to do so. This contrasts with the patients who had grunting at presentation, all of whom settled within 22 hours of ingestion before discharge, and were treatment successes. In the treatment failures, flaring developed in two patients and new crepitations were found in three patients. There were no treatment

successes with new-onset flaring at Day 3 post-ingestion. Radiographic changes which showed worsening or new features were supportive of the clinical assessment that the five patients were treatment failures.

Table 5A: Reported symptoms at the time child classified as a treatment failure

	Cough	**Wheeze**	**Shortness of breath**	**Fever**
P1	Deteriorating	Absent	Deteriorating	Static
P2	Resolved	Absent	Deteriorating	Absent
A1	Absent	Absent	Improving	Improving
P3	Static	Absent	Static	Improving
A2	Static	Static	Static	Static

P = placebo, A = active

Table 5B: Clinical signs and radiological findings at presentation (a) compared to those when treatment failure was determined (b)

		RR	Recession	Flaring	Grunting	Wheeze	Creps	Sats	Temp	CXR
P1	a	40	Mild	Present	Absent	Absent	Absent	97	37.2	Perihilar reticular pattern, bronchial wall thickening lower zones
	b	56	Resolved	Present	Present	Absent	Localised	99	37.1	Worsening confluent air-space disease in lingula and LLL
P2	a	28	Absent	Absent	Absent	Absent	Absent	nr	37.0	Bronchial wall thickening in bilateral lower lobes
	b	42	Absent	Present	Present	Absent	Localised	96	37.3	New confluent air-space disease in the LLL
A1	a	48	Moderate	Present	Absent	Present	Diffuse	98	39.1	Normal
	b	60	Mild	Present	Present	Resolved	Diffuse	96	38.9	LLL opacification
P3	a	40	Absent	Absent	Absent	Absent	Absent	97	38.0	Confluent air-space disease in the LLL
	b	57	Absent	Present	Absent	Absent	Absent	97	38.0	Worsening of LLL opacification
A2	a	46	Absent	Present	Absent	Absent	Absent	99	36.9	Normal
	b	36	Absent	Present	Absent	Absent	Localised	99	36.7	LLL air-space opacification

P = placebo, A = active, RR = respiratory rate in breaths per minute, Creps = crepitations, Sats = oximtery, nr = not recorded, Temp = temperature in degrees Celsius, CXR = chest X-ray, LLL = left lower lobe

A detailed description of the 5 treatment failures follows:

Placebo, P1: He did not vomit post-ingestion. He received a beta-2-agonist nebulisation at the clinic before referral. At presentation he had mild to moderate tachypnoea and temperature, and flaring. On auscultation, there was decreased air entry on the right base posteriorly. Initial CXR was in keeping with aspiration. He had an URTI and diarrhoea and a current child TB contact. He was admitted for overnight observation, where he remained stable. On discharge, he continued to have mild to moderate tachypnoea and fever, and flaring. At follow-up 3 days post-ingestion, his mother confirmed adherence. She reported deterioration of his cough and shortness of breath and static fever. Clinical findings confirmed deterioration with persistence of flaring since discharge, an increase in RR to 56bpm, and the development of grunting and localised crepitations. They were coupled with worsening aspiration pneumonitis on repeat CXR. He was admitted for overnight intravenous ampicillin and discharged on amoxicillin. TB investigation was positive with a reactive Mantoux (17mm) and two gastric washings negative for acid-fast bacilli. He was commenced on TB therapy and his pulmonary TB notified to the local health authority. He was HIV negative.

Placebo, P2: He presented directly to RCWMCH. He did not vomit post-ingestion. Cough and CXR changes were the only features suggestive of aspiration pneumonitis. He had a significant past respiratory history which included being born at 1250grams (one of triplets) and requiring endotracheal surfactant and continuous positive airway pressure (CPAP) ventilation. He subsequently suffered numerous lower respiratory tract infections with lower airway obstruction and positive bronchodilator response. He had no current URTI. He was observed as an ambulatory patient. He initially improved on study drug at home, but subsequently deteriorated with increasing shortness of breath prompting his mother to bring him back within 48 hours of ingestion, earlier than his first scheduled follow-up. Clinical findings confirmed deterioration with a mild tachypnoea of 42bpm, and the development of grunting, flaring, crepitations and irritability since presentation. Repeat CXR showed new features consistent with aspiration. He was placed on amoxicillin and sent home. At further follow-up, he showed improvement.

Active, A1: He was given milk post-ingestion and vomited once. Before referral from the Day Hospital, he was given a stat dose of intramuscular ampicillin 250milligrams. Clinical presentation showed mild to moderate tachypnoea, severe temperature, moderate recessions, flaring, wheeze, crepitations and drowsiness. His CXR was normal. He had no current URTI and no TB contacts. He was admitted for overnight observation, where he improved with

only localised crepitations and some irritability on discharge. At follow-up 3 days post-ingestion, his mother confirmed adherence. She reported an overall improvement in symptoms, and mild diarrhoea and vomiting. However, clinical findings of severe tachypnoea with a RR of 60bpm, severe temperature of 38.9˚C, a fruity cough, flaring, grunting, crepitations and irritability were consistent with clinical deterioration. He also had evidence of a new-onset URTI. These features were coupled with new abnormal findings on repeat CXR. He was admitted for intravenous cefuroxime and discharged with oral co-amoxiclavulanic acid. His TB (Mantoux and induced sputum) and HIV investigations were negative. Full blood count revealed a normocytic anaemia (haemoglobin 9.4, laboratory normal reference range 10.7 to 13.1 grams per litre and mean corpuscular volume 72.6, laboratory normal reference range 70.0 to 86.0 fl) for which iron and folate were prescribed. At further follow-up, he showed improvement.

Placebo, P3: She was given milk post-ingestion and vomited twice. Clinical presentation showed a mild to moderate temperature only. Her CXR showed features of pneumonitis. She had no current URTI and no TB contacts. She was observed as an ambulatory patient. At 3 days post-ingestion, the mother confirmed adherence. She reported static cough and shortness of breath and improvement in her fever. Clinical findings of severe tachypnoea with a RR of 56bpm, mild to moderate temperature of 38.0˚C, flaring and decreased air entry on the left on auscultation were evident of clinical deterioration since presentation. She also had a new-onset URTI and aphthous mouth ulcers. Repeat CXR showed worsening pneumonitis. The patient was given amoxicillin and bonjela (topical anaesthetic) and sent home. She was unfortunately lost to further follow-up; numerous attempts to contact her proved unsuccessful.

Active, A2: He was given water and milk following ingestion with no vomiting. He had mild to moderate tachypnoea and flaring. CXR was normal. He had an URTI 10 days prior to ingestion for which his mother gave him cough syrup but no antibiotic. He was observed as an ambulatory patient. He represented within 2 days with concerns of worsening cough, fever, sweating, loss of appetite and floppiness. His clinical findings of RR 28bpm, no fever and absent flaring, grunting and recessions were not suggestive of deterioration, but the on-duty doctor opted to readmit him overnight and continue on study drug. The next morning, his caregiver reported static cough, fever, wheeze and shortness of breath. Clinical findings were of a normal RR although increased from the night before to 36bpm, irritability, flaring and crepitations, which confirmed overnight deterioration. His repeat CXR now also had features consistent with aspiration pneumonitis. It was decided that he be started on intravenous ampicillin. He was transferred to a secondary level hospital, where persistent temperatures and a night of nasal-prong oxygen necessitated the addition of gentamycin to

his treatment regimen. HIV and TB (Mantoux and induced sputum) investigations were negative. Measures of infection were raised (WCC 18.00 X 10^9, laboratory normal reference range 6.00 to 18.00 X 10^9 per litre, quantitative C-reactive protein 204.6, laboratory normal reference range 0.1 to 7.5 milligrams per litre) and other sources of infection were explored (negative blood culture, normal urine dipstix). He was discharged after 4 days in hospital on co-amoxiclavulanic acid. At follow-up phone call 9 days post-ingestion the child had ongoing fever on treatment. A final call, 5 days later, found him to be fully recovered. This child did not have the clear signs of deterioration seen in the other four treatment failures, but the clinical assessment that he required a change in treatment is supported by his subsequent clinical course. There were no other patients with similar delayed recovery.

PRIMARY OBJECTIVE

Antibiotic efficacy comparing placebo versus active treatment groups

Primary outcome measure

In the placebo group, there were 32 treatment successes (32/35, 91%; 95% CI, 78 to 97) and three treatment failures (3/35, 9%; 95% CI, 3 to 22)(Table 6). In the active group, there were 37 treatment successes (37/39, 95%; 95% CI, 83 to 99) and two treatment failures (2/39, 5%; 95% CI, 1 to 17). There was no significant difference between placebo and active groups in treatment failure (relative risk (RR), 0.60; 95% CI, 0.11 to 3.37).

Table 6: Summary of outcome measures for placebo and active groups

	PLACEBO	**ACTIVE**	***P* value**
PRIMARY, *n* (%)	*n* = 35	*n* = 39	
Treatment success	32 (91)	37 (95)	>0.05
Treatment failure	3 (9)	2 (5)	>0.05
SECONDARY			
Stay in hospital (days)*	0.5 (0-1.0)	0.5 (0.5-1.0)	>0.05
Day 3 post-ingestion, *n* (%)	*n* = 24	*n* = 35	
Absent symptoms and signs	6 (25)	6 (17)	>0.05
Symptoms only	2 (8)	8 (23)	>0.05
Signs only	2 (8)	3 (9)	>0.05
Symptoms and signs	14 (58)	18 (51)	>0.05
Day 5 post-ingestion, *n* (%)	*n* = 26	*n* = 29†	
Absent symptoms and signs	5 (19)	13 (45)	>0.05
Symptoms only	13 (50)	7 (24)	>0.05
Signs only	2 (8)	4 (14)	>0.05
Symptoms and signs	6 (23)	4 (14)	>0.05

*Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = 29), data were not recorded or unknown for the missing number

Secondary outcome measures

The median length of hospital stay for placebo (0.5 days; IQR, 0 to 1.0) and active (0.5 days; IQR, 0.5 to 1.0) groups was identical ($P > 0.50$)(Table 6). There were no differences in the symptoms and signs found in the placebo and active groups on Day 3 post-ingestion (Tables 6, 7A and B).

At Day 5 post-ingestion, the only significant differences were for reported cough and recorded temperature (Tables 6, 7A and B). The importance of these results is questionable. Although the number of children with an ongoing cough was greater in the placebo group ($\chi^2_1 = 9.266$, $P < 0.01$)(Table 7A), the greater proportion was improving ($\chi^2_3 = 11.344$, $P = 0.01$)(Table 7B). Similarly, the recorded temperature in the placebo group was significantly greater (U = 250.000, Z = -2.141, $P < 0.05$)(Table 7A), but none of the children had an elevated temperature (placebo median 36.7˚C; IQR, 36.4 to 36.9 and active median 36.5˚C; IQR, 36.2 to 36.8). There were no study participants with severe RR severity or grunting at the second follow-up (Table 7A).

Table 7A: Follow-up for placebo and active groups

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	PLACEBO	**ACTIVE**	***P***	**PLACEBO**	**ACTIVE**	***P***
SYMPTOMS**,** *n* (%)	*n* = 31†	*n* = 38		*n* = 32	*n* = 36†	
Cough			>0.05			<0.05
Asymptomatic	17 (55)	21 (55)		13 (41)	27 (75)	
Symptomatic	13 (42)	17 (45)		19 (59)	8 (22)	
Wheeze			>0.05			>0.05
Asymptomatic	26 (84)	32 (84)		27 (84)	34 (94)	
Symptomatic	4 (13)	6 (16)		5 (16)	1 (3)	
Shortness of breath			>0.05			>0.05
Asymptomatic	23 (74)	31 (82)		28 (88)	34 (94)	
Symptomatic	7 (23)	7 (18)		4 (12)	1 (3)	
Fever			>0.05			>0.05
Asymptomatic	19 (61)	23 (61)		23 (72)	29 (81)	
Symptomatic	11(35)	15 (39)		9 (28)	6 (17)	
SIGNS, *n* (%)	*n* = 24	*n* = 35		*n* = 26	*n* = 29	
Respiratory rate (bpm)*	37 (33-44)	38 (32-43)	>0.05	37 (32-42)	35 (31-40)	>0.05
Respiratory rate severity			>0.05			>0.05
Mild to moderate (41-50bpm)	5 (21)	8 (23)		7 (27)	6 (21)	
Severe (> 50bpm)	4 (17)	5 (14)		0 (0)	0 (0)	
Recessions (mild)	1 (4)	1 (3)	>0.05	1 (4)	0 (0)	>0.05
Flaring	3 (13)	5 (14)	>0.05	0 (0)	1 (3)	>0.05
Grunting	2 (8)	1 (3)	>0.05	0 (0)	0 (0)	>0.05
Wheeze	3 (13)	2 (6)	>0.05	1 (4)	0 (0)	>0.05
Crepitations			>0.05			>0.05
Localised	3 (13)	6 (17)		1 (4)	2 (7)	
Diffuse	1 (4)	5 (14)		0 (0)	1 (3)	
Temperature (˚C)*	36.9 (36.5-37.5)	36.7 (36.3-37.2)	>0.05	36.7 (36.4-36.9)	36.5 (36.2-36.8)	<0.05
Temperature severity			>0.05			>0.05
Mild to moderate (37.5–38.5˚C)	5 (21)	2 (6)		0 (0)	0 (0)	
Severe (> 38.5˚C)	1 (4)	3 (9)		0 (0)	0 (0)	
Altered mental status	4 (17)	8 (23)	>0.05	1 (4)	1 (3)	>0.05

*****Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

bpm = breaths per minute

Table 7B: Description of changes in reported symptoms from previous assessment for placebo and active groups

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	PLACEBO	**ACTIVE**	***P***	**PLACEBO**	**ACTIVE**	***P***
SYMPTOMS, *n* (%)	*n* = 31*	*n* = 38		*n* = 32	*n* = 36*	
Cough			>0.05			<0.05
Absent or resolved	17 (55)	21 (55)		13 (41)	27 (75)	
Improving	7 (23)	14 (37)		13 (41)	5 (14)	
Static	3 (10)	2 (5)		3 (9)	0 (0)	
Deteriorating	3 (10)	1 (3)		3 (9)	3 (8)	
Wheeze			>0.05			>0.05
Absent or resolved	26 (84)	32 (84)		27 (84)	34 (94)	
Improving	3 (10)	4 (11)		3 (9)	0 (0)	
Static	1 (3)	2 (5)		0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)		2 (6)	1 (3)	
Shortness of breath			>0.05			>0.05
Absent or resolved	23 (74)	31 (82)		28 (88)	34 (94)	
Improving	4 (13)	4 (11)		3 (9)	0 (0)	
Static	1 (3)	3 (8)		0 (0)	0 (0)	
Deteriorating	2 (6)	0 (0)		1 (3)	1 (3)	
Fever			>0.05			>0.05
Absent or resolved	19 (61)	23 (61)		23 (72)	29 (81)	
Improving	7 (23)	10 (26)		5 (16)	4 (11)	
Static	4 (13)	4 (11)		2 (6)	0 (0)	
Deteriorating	0 (0)	1 (3)		2 (6)	2 (6)	

*****Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

Comparison of treatment success and failure

As there was no evidence of treatment differences, the placebo and active groups were combined and analysed by treatment success and failure, to identify possible risk factors at enrolment for treatment failure. This also enabled investigation of possible confounding conditions which might produce similar symptoms and signs to kerosene-associated pneumonitis and therefore lead children to be incorrectly classified as a treatment failure.

There were no differences in baseline characteristics, ingestion event details (Table 8) or presenting clinical parameters (Table 9) between treatment success and failure. The initial length of stay in hospital was similar in these groups (treatment success median 0.5 days, IQR, 0 to 1.0; treatment failure median 0 days, IQR, 0 to 0.5; $P > 0.05$).

Table 8: Baseline characteristics and event details for treatment success and failure

	TREATMENT SUCCESS *n* = 69	**TREATMENT FAILURE *n* = 5**	***P* value**
PATIENT MEASUREMENTS			
Male:female, *n* (%)	41:28 (59:41)	4:1 (80:20)	>0.05
Age (months)*	19 (16-22)	19 (16-30)	>0.05
Weight (kg)*	11.5 (10.0-12.8)	12.3 (11.4-13.2)	>0.05
INGESTION EVENT, *n* (%)			
Hours post-ingestion at enrolment*	6.0 (3.5-8.0)	8.5 (3.5-15.0)	>0.05
Season			>0.05
Spring	16 (23)	2 (40)	
Summer	18 (26)	3 (60)	
Autumn	11 (16)	0 (0)	
Winter	24 (35)	0 (0)	
Witnessed	23 (33)	1 (20)	>0.05
Occurred at home	43 (62)	3 (60)	>0.05
Container			>0.05
Paraffin bottle	19 (28)	1 (20)	
Juice bottle	38 (55)	4 (80)	
Other (paraffin lamp)	3 (4)	0 (0)	
Given milk and/or water at place of ingestion	49 (71)	3 (60)	>0.05

*Values are median (interquartile range)

Table 9: Clinical presentation for treatment success and failure

	TREATMENT SUCCESS *n* = 69	**TREATMENT FAILURE *n* = 5**	***P* value**
INCLUSION CRITERIA, *n* (%)			
Symptoms only	11 (16)	2 (40)	>0.05
Signs only	3 (4)	0 (0)	>0.05
Symptoms and signs	55 (80)	3 (60)	>0.05
SYMPTOMS, *n* (%)			
History of coughing	66 (96)	5 (100)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	46 (36-58)	40 (34-47)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	19 (28)	2 (40)	
Severe (> 50bpm)	22 (32)	0 (0)	
Recessions			>0.05
Mild	15 (22)	1 (20)	
Moderate	3 (4)	1 (20)	
Flaring	21 (30)	3 (60)	>0.05
Grunting	12 (17)	0 (0)	>0.05
Wheeze	6 (9)	1 (20)	>0.05
Crepitations			>0.05
Localised	9 (13)	0 (0)	
Diffuse	11 (16)	1 (20)	
Oximetry (%saturation)*	99 (97-99)	98 (97-99)	>0.05
Temperature (˚C)*	37.2 (36.7-38.2)	37.2 (37.0-38.6)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	14 (20)	1 (20)	
Severe (> 38.5˚C)	14 (20)	1 (20)	
Altered mental status	18 (26)	1 (20)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

The symptoms and signs of treatment failure were recorded at the point of alteration of treatment: Day 3 post-ingestion for four treatment failures and 48 hours post-ingestion for the other treatment failure. These findings were compared to the Day 3 symptoms and signs of treatment success. As expected from the definition of treatment success and failure, symptoms and signs were more severe for treatment failure (Tables 10A and B). They were reported cough (χ^2_3 = 11.562, P < 0.01) and shortness of breath (χ^2_3 = 40.476, P < 0.001) (Table 10B) and the presence of flaring (Fischer, P < 0.001), grunting (Fischer, P < 0.001) and crepitations (χ^2_2 = 9.871, P < 0.01)(Table 10A). Although there was a difference in recorded RR (U = 48.000, Z = -2.374, P < 0.05) between success (median 37bpm, IQR, 32 to 42) and failure (median 56bpm, IQR, 39 to 59), there was no difference in the presence of tachypnoea. However, of those who were tachypnoeic, a significantly greater proportion of failures (60%) were in the severe RR category compared to successes (11%) (χ^2_3 = 8.770, P < 0.05). The differences in recorded temperatures (U = 59.000, Z = -2.073, P < 0.05) between success (median 36.7˚C, IQR, 36.3 to 37.2) and failure (median 37.3˚C, IQR, 36.9 to 38.5), were not relevant as there were no differences in the presence of fever or temperature severity.

Table 10A: Comparison of symptoms and signs for treatment success at Day 3 post-ingestion and treatment failure at the point of alteration of treatment

	TREATMENT SUCCESS	TREATMENT FAILURE	*P* value
SUMMARY, *n* (%)	*n* = 54†	*n* = 5	
Absent symptoms and signs	12 (22)	0 (0)	>0.05
Symptoms only	10 (19)	0 (0)	>0.05
Signs only	4 (7)	0 (0)	>0.05
Symptoms and signs	27 (50)	5 (100)	>0.05
SYMPTOMS**,** *n* (%)	*n* = 64†	*n* = 5	
Cough			<0.05
Asymptomatic	36 (56)	2 (40)	
Symptomatic	27 (42)	3 (60)	
Wheeze			>0.05
Asymptomatic	54 (84)	4 (80)	
Symptomatic	9 (14)	1 (20)	
Shortness of breath			<0.05
Asymptomatic	54 (84)	0 (0)	
Symptomatic	9 (14)	5 (100)	
Fever			>0.05
Asymptomatic	41 (64)	1 (20)	
Symptomatic	22 (34)	4 (80)	
SIGNS, *n* (%)	*n* = 54	*n* = 5	
Respiratory rate (bpm)*	37 (32-42)	56 (39-59)	<0.05
Respiratory rate severity			<0.05
Mild to moderate (41-50bpm)	12 (22)	1 (20)	
Severe (> 50bpm)	6 (11)	3 (60)	
Recessions (mild)	1 (2)	1 (20)	>0.05
Flaring	3 (6)	5 (100)	<0.05
Grunting	0 (0)	3 (60)	<0.05
Wheeze	5 (9)	0 (0)	>0.05
Crepitations			<0.05
Localised	6 (11)	3 (60)	
Diffuse	5 (9)	1 (20)	
Temperature (˚C)*	36.7 (36.3-37.2)	37.3 (36.9-38.5)	<0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	6 (11)	1 (20)	
Severe (> 38.5˚C)	3 (6)	1 (20)	
Altered mental status	9 (17)	3 (60)	>0.05

*Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms/summary), data were not recorded or unknown for the missing number

bpm = breaths per minute

Table 10B: Description of changes in reported symptoms from previous assessment for treatment success at Day 3 post-ingestion and treatment failure at the point of alteration of treatment

	TREATMENT SUCCESS	**TREATMENT FAILURE**	***P* value**
SYMPTOMS**,** *n* (%)	*n* = 64*	*n* = 5	
Cough			<0.05
Absent or resolved	36 (56)	2 (40)	
Improving	21 (33)	0 (0)	
Static	3 (5)	2 (40)	
Deteriorating	3 (5)	1 (20)	
Wheeze			>0.05
Absent or resolved	54 (84)	4 (80)	
Improving	7 (11)	0 (0)	
Static	2 (3)	1 (20)	
Deteriorating	0 (0)	0 (0)	
Shortness of breath			<0.05
Absent or resolved	54 (84)	0 (0)	
Improving	7 (11)	1 (20)	
Static	2 (2)	2 (40)	
Deteriorating	0 (0)	2 (40)	
Fever			>0.05
Absent or resolved	41 (64)	1 (20)	
Improving	15 (23)	2 (40)	
Static	6 (9)	2 (40)	
Deteriorating	1 (2)	0 (0)	

*Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

SECONDARY OBJECTIVES

Confounding conditions and risk factors for severity and outcome

Treatment failure

URTI and active TB disease, two possible confounding conditions, were similar in both treatment success and failure groups (Table 11). The only significant risk factor for treatment failure was residence in formal housing (Fischer, $P < 0.05$). Linear regression modelling of factors for treatment failure showed only housing as significant (Table 12).

Table 11: Confounding conditions and risk factors for treatment failure

	TREATMENT SUCCESS ***n*** **= 69**	**TREATMENT FAILURE** ***n*** **= 5**	***P*** **value**
POSSIBLE CONFOUNDING CONDITIONS**,** *n* (%)			
Upper respiratory tract infection (URTI)			>0.05
Preceding	15 (22)	2 (40)	
New-onset	29 (42)	2 (40)	
Active TB disease	2 (3)	1 (20)	>0.05
POSSIBLE RISK FACTORS**,** *n* (%)			
Vomiting post-ingestion	39 (57)	2 (40)	>0.05
Age categories (months)			>0.05
12-23	55 (80)	3 (60)	
24-35	11 (16)	2 (40)	
> 36	3 (4)	0 (0)	
Smoking contact	25 (36)	1 (20)	>0.05
HIV exposed*	20 (29)	0 (0)	>0.05
Prior respiratory history	16 (23)	1 (20)	>0.05
Formal housing	19 (28)	4 (80)	<0.05
Electricity	47 (68)	4 (80)	>0.05
Educational status (mother)			>0.05
< 10 years formal education	16 (23)	2 (40)	
> 10 years formal education	43 (62)	2 (40)	
Tertiary	10 (14)	1 (20)	

*As there was only 1 HIV-infected child (treatment success), she was included in the analysis according to HIV-exposure status (exposed versus unexposed)

Table 12: Linear regression analysis of possible confounding conditions and risk factors for treatment failure

RISK FACTOR	Wald Chi-Square	Degrees of freedom	*P* value
Vomiting	0.031	1	0.860
Smoking contact	0.077	1	0.781
URTI	0.249	2	0.883
Prior respiratory history	0.345	1	0.557
Active TB disease	2.055	1	0.152
Season	1.766	3	0.622
Formal housing	3.998	1	0.046

Analysis of confounding conditions

A history of preceding URTI resulted in a few significant differences at presentation (Table 13A). Vomiting after ingestion was more frequent in those without URTI (63%) than those with a preceding URTI (29%)($\chi^2_1 = 6.442$, $P < 0.05$). In contrast, flaring was more common in those with a preceding URTI (59%) than those without (25%)($\chi^2_1 = 6.761$, $P < 0.01$).

At follow-up visits, the groups were analysed according to categories of absent, preceding and new-onset URTI (Table 13B). At Day 3 post-ingestion, there was no difference in reported symptoms. The difference in recorded temperature (K-W $\chi^2_2 = 7.320$, $P < 0.05$) between those with absent URTI (median 36.7˚C, IQR, 36.1 to 37.2), a preceding URTI (median 36.4˚C, IQR, 36.2 to 36.8) and new-onset URTI (median 36.9˚C, IQR, 36.6 to 37.9), was not relevant as there were no differences in the presence of fever or temperature severity. At Day 5 post-ingestion, there was a greater proportion with reported ongoing fever in those with preceding (27%) and new-onset (31%) URTI than absent URTI (8%)($\chi^2_6 = 12.965$, $P < 0.05$).

Table 13A: Clinical presentation according to the presence of an upper respiratory tract infection (URTI)

	Absent URTI *n* = 57	**Preceding URTI *n* = 17**	***P* value**
SYMPTOMS, *n* (%)			
History of coughing	54 (95)	17 (100)	>0.05
History of vomiting	36 (63)	5 (29)	<0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	48 (37-58)	42 (35-50)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	16 (28)	5 (29)	
Severe (> 50bpm)	19 (33)	3 (18)	
Recessions			>0.05
Mild	13 (23)	3 (18)	
Moderate	4 (7)	0 (0)	
Flaring	14 (25)	10 (59)	<0.05
Grunting	9 (16)	3 (18)	>0.05
Wheeze	2 (4)	0 (0)	>0.05
Crepitations			>0.05
Localised	7 (12)	2 (12)	
Diffuse	10 (18)	2 (12)	
Temperature (˚C)*	37.2 (36.8-38.5)	37.2 (36.3-37.7)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	11 (19)	4 (24)	
Severe (> 38.5˚C)	15 (26)	0 (0)	
Altered mental status	16 (28)	3 (18)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

Table 13B: Follow-up according to absent, preceding or new-onset upper respiratory tract infection (URTI)

	DAY 3 POST-INGESTION				DAY 5 POST-INGESTION			
	Absent	**Preceding**	**New-onset**	***P***	**Absent**	**Preceding**	**New-onset**	***P***
SYMPTOMS, *n* (%)	*n* = 24	*n* = 16†	*n* = 29		*n* = 24	*n* = 15	*n* = 29†	
Cough				>0.05				>0.05
Absent or resolved	15 (63)	6 (38)	17 (59)		20 (83)	7 (47)	13 (45)	
Improving	8 (33)	6 (38)	7 (24)		2 (8)	6 (40)	10 (34)	
Static	1 (4)	1 (6)	3 (10)		1 (4)	1 (7)	1 (3)	
Deteriorating	0 (0)	2 (13)	2 (7)		1 (4)	1 (7)	4 (14)	
Wheeze				>0.05				>0.05
Absent or resolved	20 (83)	14 (88)	24 (83)		22 (92)	12 (80)	27 (93)	
Improving	4 (17)	0 (0)	3 (10)		1 (4)	1 (7)	1 (3)	
Static	0 (0)	1 (6)	2 (7)		0 (0)	0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)	0 (0)		1 (4)	2 (13)	0 (0)	
Shortness of breath				>0.05				>0.05
Absent or resolved	20 (83)	13 (81)	21 (72)		23 (96)	15 (100)	24 (83)	
Improving	2 (8)	0 (0)	6 (21)		0 (0)	0 (0)	3 (10)	
Static	1 (4)	1 (6)	2 (7)		0 (0)	0 (0)	0 (0)	
Deteriorating	1 (4)	1 (6)	0 (0)		1 (4)	0 (0)	1 (3)	
Fever				>0.05				<0.05
Absent or resolved	19 (79)	8 (50)	15 (52)		22 (92)	11 (73)	19 (66)	
Improving	5 (21)	3 (19)	9 (31)		1 (4)	1 (7)	7 (24)	
Static	0 (0)	4 (25)	4 (14)		0 (0)	2 (13)	0 (0)	
Deteriorating	0 (0)	0 (0)	1 (3)		1 (4)	1 (7)	2 (7)	

SIGNS, *n* (%)	*n* = 20	*n* = 14	*n* = 25		*n* = 16	*n* = 13	*n* = 26	
Respiratory rate (bpm)*	35 (30-42)	37 (32-41)	41 (34-51)	>0.05	34 (29-40)	35 (29-41)	38 (34-43)	>0.05
Respiratory rate severity				>0.05				>0.05
Mild to moderate (41-50bpm)	4 (20)	2 (14)	7 (28)		2 (13)	3 (23)	8 (31)	
Severe (> 50bpm)	2 (10)	1 (7)	6 (24)		0 (0)	0 (0)	0 (0)	
Recessions (mild)	1 (5)	0 (0)	1 (4)	>0.05	0 (0)	0 (0)	1 (4)	>0.05
Flaring	3 (15)	2 (14)	3 (12)	>0.05	1 (6)	0 (0)	0 (0)	>0.05
Grunting	1 (5)	1 (7)	1 (4)	>0.05	0 (0)	0 (0)	0 (0)	>0.05
Wheeze	0 (0)	2 (14)	3 (12)	>0.05	0 (0)	1 (8)	0 (0)	>0.05
Crepitations				>0.05	0 (0)	1 (8)	2 (8)	>0.05
Localised	4 (20)	3 (21)	2 (8)					
Diffuse	0 (0)	1 (7)	5 (20)		0 (0)	1 (8)	0 (0)	
Temperature (˚C)*	36.7 (36.1-37.2)	36.4 (36.2-36.8)	36.9 (36.6-37.9)	<0.05	36.4 (36.1-36.6)	36.6 (36.3-36.8)	36.8 (36.5-36.9)	>0.05
Temperature severity				>0.05				>0.05
Mild to moderate (37.5–38.5˚C)	2 (10)	2 (14)	3 (12)		0 (0)	0 (0)	0 (0)	
Severe (> 38.5˚C)	0 (0)	0 (0)	4 (16)		0 (0)	0 (0)	0 (0)	
Altered mental status	3 (15)	4 (29)	5 (20)	>0.05	0 (0)	0 (0)	1 (4)	>0.05

*Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

bpm = breaths per minute

There were no patients with a history of prior TB infection. Of the patients with current TB contacts (n = 10; seven placebo, three active) only one, who was HIV positive on highly active antiretroviral treatment (HAART), had been on TB prophylaxis. Three of the remaining nine were known to have been investigated for TB. Another child's mother had recently submitted sputum for TB investigation; the results were still pending at enrolment and could not be located at the local laboratory.

During the study, 16 patients (eight placebo, eight active) required TB investigation; three (4%) were diagnosed with active TB disease. One newly diagnosed patient (placebo) was investigated for TB as he was a treatment failure (see previous details). Another newly-diagnosed patient (active) was investigated due to a current TB contact. He had a reactive Mantoux (17mm). Induced sputum and nasopharyngeal aspirate were negative for acid-fast bacilli. Symptoms at Day 5 post-ingestion were attributed to asthma co-morbidity with weather-related bronchospasm necessitating use of his salbutamol metered-dose inhaler (MDI). The third newly-diagnosed patient (placebo) had a current TB contact and suggestive CXR with perihilar and mediastinal lymph nodes and bronchus compression. His Mantoux was non-reactive and two gastric washings were negative for acid-fast bacilli, but he was started empirically on TB treatment and prednisone.

All newly-diagnosed patients were commenced on appropriate TB therapy and notified to the local health authority. The clinical presentation between those diagnosed with active TB disease and those without showed no differences (Table 14A). At Day 3 post-ingestion, a greater proportion of patients with active TB disease reported deteriorating shortness of breath (χ^2_3 = 10.474, $P < 0.05$) and static fever (χ^2_3 = 9.283, $P < 0.05$)(Table 14B). Day 5 follow-up showed a greater proportion of patients with active TB disease (50%) with ongoing symptoms: cough (χ^2_3 = 15.204, $P < 0.005$), wheeze (χ^2_2 = 10.015, $P < 0.01$), shortness of breath (χ^2_2 = 15.761, $P < 0.001$) and fever (χ^2_3 = 15.868, P = 0.001). The relevance of these differences in symptoms is questionable as there were so few patients diagnosed with active TB disease. There was no difference in clinical findings between groups at either follow-up.

Table 14A: Clinical presentation according to active *Mycobacterium tuberculosis* (TB) disease

	No TB ***n* = 71**	**Active TB** ***n* = 3**	***P* value**
SYMPTOMS, *n* (%)			
History of coughing	68 (96)	3 (100)	>0.05
History of vomiting	39 (55)	2 (67)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	45 (36-58)	45 (40-45)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	20 (28)	1 (33)	
Severe (> 50bpm)	22 (31)	0 (0)	
Recessions			>0.05
Mild	15 (21)	1 (33)	
Moderate	4 (6)	0 (0)	
Flaring	23 (32)	1 (33)	>0.05
Grunting	12 (17)	0 (0)	>0.05
Wheeze	7 (10)	0 (0)	>0.05
Crepitations			>0.05
Localised	8 (11)	1 (33)	
Diffuse	12 (17)	0 (0)	
Temperature (˚C)*	37.2 (36.7-38.2)	37.2 (36.4-37.2)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	15 (21)	0 (0)	
Severe (> 38.5˚C)	15 (21)	0 (0)	
Altered mental status	18 (25)	1 (33)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

Table 14B: Follow-up according to active *Mycobacterium tuberculosis* (TB) disease

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	No TB	**Active TB**	***P***	**No TB**	**Active TB**	***P***
SYMPTOMS, *n* (%)	*n* = 66†	*n* = 3		*n* = 66†	*n* = 2	
Cough			>0.05			<0.05
Absent or resolved	37 (56)	1 (33)		40 (61)	0 (0)	
Improving	20 (30)	1 (33		18 (27)	0 (0)	
Static	5 (8)	0 (0)		2 (3)	1 (50)	
Deteriorating	3 (5)	1 (33)		5 (8)	1 (50)	
Wheeze			>0.05			<0.05
Absent or resolved	55 (83)	3 (100)		60 (91)	1 (50)	
Improving	7 (11)	0 (0)		3 (5)	0 (0)	
Static	3 (5)	0 (0)		0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)		2 (3)	1 (50)	
Shortness of breath			<0.05			<0.05
Absent or resolved	52 (79)	2 (67)		61 (92)	1 (50)	
Improving	8 (12)	0 (0)		3 (5)	0 (0)	
Static	4 (6)	0 (0)		0 (0)	0 (0)	
Deteriorating	1 (2)	1 (33)		1 (2)	1 (50)	
Fever			<0.05			<0.05
Absent or resolved	41 (62)	1 (33)		51 (77)	1 (50)	
Improving	17 (26)	0 (0)		9 (14)	0 (0)	
Static	6 (9)	2 (67)		1 (2)	1 (50)	
Deteriorating	1 (2)	0 (0)		4 (6)	0 (0)	
SIGNS, *n* (%)	*n* = 56	*n* = 3		*n* = 53	*n* = 2	
Respiratory rate (bpm)*	38 (32-43)	48 (34-48)	>0.05	36 (32-41)	31 (25-31)	>0.05
Respiratory rate severity			>0.05			>0.05
Mild to moderate (41-50bpm)	12 (21)	1 (33)		13 (25)	0 (0)	
Severe (> 50bpm)	8 (14)	1 (33)		0 (0)	0 (0)	
Recessions (mild)	2 (4)	0 (0)	>0.05	1 (2)	0 (0)	>0.05
Flaring	7 (13)	1 (33)	>0.05	1 (2)	0 (0)	>0.05
Grunting	2 (4)	1 (33)	>0.05	0 (0)	0 (0)	>0.05
Wheeze	5 (9)	0 (0)	>0.05	1 (2)	0 (0)	>0.05
Crepitations			>0.05			>0.05
Localised	8 (14)	1 (33)		3 (6)	0 (0)	
Diffuse	6 (11)	0 (0)		1 (2)	0 (0)	
Temperature (˚C)*	36.8 (36.4-37.3)	37 (36.2-37.0)	>0.05	36.5 (36.3-36.9)	36.5 (36.4-36.5)	>0.05
Temperature severity			>0.05			>0.05
Mild to moderate (37.5–38.5˚C)	7 (13)	0 (0)		0 (0)	0 (0)	
Severe (> 38.5˚C)	4 (7)	0 (0)		0 (0)	0 (0)	
Altered mental status	11 (20)	1 (33)	>0.05	2 (4)	0 (0)	>0.05

*Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

bpm = breaths per minute

Analysis of risk factors

There were no differences in clinical presentation or symptoms and signs at follow-up between those patients who vomited post-ingestion and those who did not (Appendix F1and 2). In only one patient, it was not known if he vomited post-ingestion.

Younger age played a significant role in the clinical presentation of RR, RR severity and tachypnoea (Table 15A). Children under 2 years showed a significantly larger proportion with tachypnoea ($\chi^2_2 = 11.510$, $P < 0.005$) and increased RR severity ($\chi^2_4 = 14.250$, $P < 0.01$) with differences for recorded RR (K-W $\chi^2_2 = 9.321$, $P < 0.01$) between the age groups (1to 2 years: median 48bpm, IQR, 40 to 60; 2 to 3 years: median 39bpm, IQR, 31 to 47; >3 years: median 31bpm, IQR, 30 to 31). At Day 3 post-ingestion, there was a significantly greater proportion of children over the age of 3 years with deterioration in reported fever ($\chi^2_6 = 36.033$, $P < 0.001$)(Table 15B).

The presence of a household smoking contact (unknown in two patients) did not impact on clinical presentation or Day 3 post-ingestion (Appendix G1 and 2). At Day 5 post-ingestion, there was a difference in recorded RR (U = 214.500, Z = -2.144, $P < 0.05$) for those with a smoking contact (median 38bpm, IQR, 35 to 44) and those without (median 35bpm, IQR, 28 to 40), but not for tachypnoea or RR severity. Similarly, there was a difference in recorded temperatures (U = 221.000, Z = -2.027, $P < 0.05$) for those with a smoking contact (median 36.7˚C, IQR, 36.5 to 37.0) and those without (median 36.5˚C, IQR, 36.2 to 36.8), but not for fever or temperature severity. The relevance of the minor differences between RR and recorded temperature is questionable as similar differences were not reflected when categorised.

Table 15A: Clinical presentation according to age groups

	1-2 years ***n*** **= 58**	**2-3 years** ***n*** **= 13**	**>3 years** ***n*** **= 3**	***P*** **value**
SYMPTOMS, *n* (%)				
History of coughing	55 (95)	13 (100)	3 (100)	>0.05
History of vomiting	31 (53)	7 (54)	3 (100)	>0.05
SIGNS, *n* (%)				
Respiratory rate (bpm)*	48 (40-60)	39 (31-47)	31 (30-31)	<0.05
Respiratory rate severity				<0.05
Mild to moderate (41-50bpm)	17 (29)	4 (31)	0 (0)	
Severe (> 50bpm)	22 (38)	0 (0)	0 (0)	
Recessions				>0.05
Mild	15 (26)	1 (8)	0 (0)	
Moderate	4 (7)	0 (0)	0 (0)	
Flaring	20 (34)	3 (23)	1 (33)	>0.05
Grunting	10 (17)	2 (15)	0 (0)	>0.05
Wheeze	7 (12)	0 (0)	0 (0)	>0.05
Crepitations				>0.05
Localised	7 (12)	2 (15)	0 (0)	
Diffuse	11 (19)	0 (0)	1 (33)	
Temperature (˚C)*	37.4 (36.8-38.4)	37.0 (36.5-37.6)	36.4 (36.0-36.4)	>0.05
Temperature severity				>0.05
Mild to moderate (37.5–38.5˚C)	12 (21)	3 (23)	0 (0)	
Severe (> 38.5˚C)	4 (7)	0 (0)	1 (33)	
Altered mental status	17 (29)	1 (8)	1 (33)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

Table 15B: Follow-up according to age groups

	DAY 3 POST-INGESTION				DAY 5 POST-INGESTION			
	1-2 years	**2-3 years**	**>3 years**	***P***	**1-2 years**	**2-3 years**	**>3 years**	***P***
SYMPTOMS, *n* (%)	*n* = 54	*n* = 12	*n* = 3†		*n* = 54†	*n* = 11	*n* = 3	
Cough				>0.05				>0.05
Absent or resolved	30 (56)	7 (58)	1 (33)		32 (59)	7 (64)	1 (33)	
Improving	17 (31)	3 (25)	1 (33)		13 (24)	3 (27)	2 (67)	
Static	4 (7)	1 (8)	0 (0)		3 (6)	0 (0)	0 (0)	
Deteriorating	3 (6)	1 (8)	0 (0)		5 (9)	1 (9)	0 (0)	
Wheeze				>0.05				>0.05
Absent or resolved	45 (83)	11 (92)	2 (67)		49 (91)	9 (82)	3 (100)	
Improving	6 (11)	1 (8)	0 (0)		2 (4)	1 (9)	0 (0)	
Static	3 (6)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)	0 (0)		2 (4)	1 (9)	0 (0)	
Shortness of breath				>0.05				>0.05
Absent or resolved	43 (80)	10 (83)	1 (33)		49 (91)	10 (91)	3 (100)	
Improving	7 (13)	0 (0)	1 (33)		3 (6)	0 (0)	0 (0)	
Static	3 (6)	1 (8)	0 (0)		0 (0)	0 (0)	0 (0)	
Deteriorating	1 (2)	1 (8)	0 (0)		1 (2)	1 (9)	0 (0)	
Fever				<0.05				>0.05
Absent or resolved	32 (59)	9 (75)	1 (33)		40 (74)	11 (100)	1 (33)	
Improving	14 (26)	3 (25)	0 (0)		8 (15)	0 (0)	1 (33)	
Static	8 (15)	0 (0)	0 (0)		2 (4)	0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)	1 (33)		3 (6)	0 (0)	1 (33)	
SIGNS, *n* (%)	*n* = 46	*n* = 11	*n* = 2		*n* = 44	*n* = 9	*n* = 2	
Respiratory rate (bpm)*	38 (32-43)	38 (30-42)	37 (24-37)	>0.05	37 (32-41)	32 (25-42)	29 (24-29)	>0.05
Respiratory rate severity				>0.05				>0.05
Mild to moderate (41-50bpm)	11 (24)	1 (9)	1 (50)		11 (25)	2 (22)	0 (0)	
Severe (> 50bpm)	7 (15)	2 (18)	0 (0)		0 (0)	0 (0)	0 (0)	
Recessions (mild)	2 (4)	0 (0)	0 (0)	>0.05	1 (2)	0 (0)	0 (0)	>0.05
Flaring	5 (11)	3 (27)	0 (0)	>0.05	0 (0)	1 (11)	0 (0)	>0.05

Grunting	2 (4)	1 (9)	0 (0)	>0.05	0 (0)	0 (0)	0 (0)	>0.05
Wheeze	4 (9)	1 (9)	0 (0)	>0.05	1 (2)	0 (0)	0 (0)	>0.05
Crepitations				>0.05				>0.05
Localised	7 (15)	2 (18)	0 (0)		3 (7)	0 (0)	0 (0)	
Diffuse	5 (11)	1 (9)	0 (0)		0 (0)	1 (11)	0 (0)	
Temperature (˚C)*	36.8 (36.4-37.1)	37.0 (36.2-37.3)	37.5 (36.0-37.5)	>0.05	36.5 (36.3-36.9)	36.6 (36.2-36.8)	37.2 (37.0-37.2)	>0.05
Temperature severity				>0.05				>0.05
Mild to moderate (37.5–38.5˚C)	5 (11)	2 (18)	0 (0)		0 (0)	0 (0)	0 (0)	
Severe (> 38.5˚C)	3 (7)	0 (0)	1 (50)		0 (0)	0 (0)	0 (0)	
Altered mental status	10 (22)	1 (9)	1 (50)	>0.05	2 (5)	0 (0)	0 (0)	>0.05

*Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

bpm = breaths per minute

There was one HIV-infected patient; therefore all patients including the HIV-infected girl were analysed according to HIV-exposure status (exposed versus unexposed). Patients who were HIV exposed (exposure status unknown in two patients) had a significantly greater proportion with diffuse crepitations at presentation ($\chi^2_2 = 7.619$, $P < 0.05$)(Table 16A). At Day 5 post-ingestion, the opposite was found with a greater proportion who were HIV unexposed with diffuse crepitations ($\chi^2_2 = 7.101$, $P < 0.05$)(Table 16B). At second follow-up there was also a significant difference in recorded RR (U = 162.500, Z = -2.744, $P < 0.01$) between those HIV exposed (median 40bpm, IQR, 36 to 44) and those not (median 33bpm, IQR, 28 to 40), but not for RR severity or tachypnoea.

Table 16A: Clinical presentation according to HIV exposure status

	HIV unexposed *n* = 52†	**HIV exposed *n* = 20†**	***P* value**
SYMPTOMS, *n* (%)			
History of coughing	50 (96)	20 (100)	>0.05
History of vomiting	26 (50)	14 (70)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	46 (36-56)	43 (37-60)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	15 (29)	5 (25)	
Severe (> 50bpm)	15 (29)	6 (30)	
Recessions			>0.05
Mild	10 (19)	6 (30)	
Moderate	2 (4)	2 (10)	
Flaring	17 (33)	7 (35)	>0.05
Grunting	9 (17)	3 (15)	>0.05
Wheeze	4 (8)	3 (15)	>0.05
Crepitations			<0.05
Localised	8 (15)	1 (5)	
Diffuse	5 (10)	7 (35)	
Temperature (˚C)*	37.2 (36.7-38.2)	37.8 (36.7-38.4)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	9 (17)	6 (30)	
Severe (> 38.5˚C)	10 (19)	5 (25)	
Altered mental status	14 (27)	5 (25)	>0.05

*Values are median (interquartile range)
†Total does not add up to 74 as two study participants had an unknown HIV exposure status
bpm = breaths per minute

Table 16B: Follow-up according to HIV exposure status

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	HIV unexposed	**HIV exposed**	***P***	**HIV unexposed**	**HIV exposed**	***P***
SYMPTOMS, *n* (%)†	*n* = 48‡	*n* = 19		*n* = 46‡	*n* = 20	
Cough			>0.05			>0.05
Absent or resolved	22 (46)	14 (74)		27 (59)	11 (55)	
Improving	17 (35)	4 (21)		13 (28)	5 (25)	
Static	5 (10)	0 (0)		2 (4)	1 (5)	
Deteriorating	3 (6)	1 (5)		3 (7)	3 (15)	
Wheeze			>0.05			>0.05
Absent or resolved	38 (79)	18 (95)		42 (91)	17 (85)	
Improving	6 (13)	1 (5)		2 (4)	1 (5)	
Static	3 (6)	0 (0)		0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)		1 (2)	2 (10)	
Shortness of breath			>0.05			>0.05
Absent or resolved	36 (75)	16 (84)		43 (93)	17 (85)	
Improving	5 (10)	3 (16)		1 (2)	2 (10)	
Static	4 (8)	0 (0)		0 (0)	0 (0)	
Deteriorating	2 (4)	0 (0)		1 (2)	1 (5)	
Fever			>0.05			>0.05
Absent or resolved	27 (56)	13 (68)		33 (72)	17 (85)	
Improving	13 (27)	4 (21)		8 (17)	1 (5)	
Static	6 (13)	2 (11)		1 (2)	1 (5)	
Deteriorating	1 (2)	0 (0)		3 (7)	1 (5)	
SIGNS, *n* (%)†	*n* = 43	*n* = 15		*n* = 36	*n* = 17	
Respiratory rate (bpm)*	36 (32-43)	38 (32-45)	>0.05	33 (28-40)	40 (36-44)	<0.05
Respiratory rate severity			>0.05			>0.05
Mild to moderate (41-50bpm)	8 (19)	5 (33)		6 (17)	6 (35)	
Severe (> 50bpm)	7 (16)	2 (13)		0 (0)	0 (0)	
Recessions (mild)	2 (5)	0 (0)	>0.05	0 (0)	1 (6)	>0.05
Flaring	7 (16)	1 (7)	>0.05	1 (3)	0 (0)	>0.05
Grunting	3 (7)	0 (0)	>0.05	0 (0)	0 (0)	>0.05
Wheeze	2 (5)	3 (20)	>0.05	0 (0)	1 (6)	>0.05
Crepitations			>0.05			<0.05
Localised	6 (14)	2 (13)		0 (0)	3 (18)	
Diffuse	5 (12)	1 (7)		1 (3)	0 (0)	
Temperature (˚C)*	36.7 (36.3-37.2)	36.9 (36.5-37.5)	>0.05	36.6 (36.2-36.9)	36.6 (36.5-36.9)	>0.05
Temperature severity			>0.05			>0.05
Mild to moderate (37.5–38.5˚C)	4 (9)	3 (20)		0 (0)	0 (0)	
Severe (> 38.5˚C)	2 (5)	2 (13)		0 (0)	0 (0)	
Altered mental status	10 (23)	2 (13)	>0.05	1 (3)	1 (6)	>0.05

*Values are median (interquartile range)

†Totals (symptoms and signs) are missing two patients whose HIV exposure status was unknown

‡Where values do not add up to the denominator (*n* = symptoms), data were not recorded for the missing number

bpm = breaths per minute

In patients with a prior respiratory history (Table 17), a significantly smaller proportion of patients (12%) were flaring at presentation compared to those without a prior respiratory history (39%)(χ^2_1 = 3.855, P = 0.05). There was a significantly smaller proportion with severe RR severity at presentation in those with a prior respiratory history (7%) than in those without (38%)(χ^2_2 = 7.507, P < 0.05). However, there were no differences for recorded RR or tachypnoea. There were no further differences at follow-up (Appendix H).

Table 17: Clinical presentation according to a prior respiratory history

	No respiratory history ***n*** **= 57**	**Respiratory history** ***n*** **= 17**	***P*** **value**
SYMPTOMS, *n* (%)			
History of coughing	55 (96)	16 (94)	>0.05
History of vomiting	31 (54)	10 (59)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	47 (36-60)	44 (34-49)	>0.05
Respiratory rate severity			<0.05
Mild to moderate (41-50bpm)	13 (23)	8 (47)	
Severe (> 50bpm)	21 (37)	1 (6)	
Recessions			>0.05
Mild	14 (25)	2 (12)	
Moderate	4 (7)	0 (0)	
Flaring	22 (39)	2 (12)	<0.05
Grunting	10 (18)	2 (12)	>0.05
Wheeze	6 (11)	1 (6)	>0.05
Crepitations			>0.05
Localised	8 (14)	1 (6)	
Diffuse	8 (14)	4 (24)	
Temperature (˚C)*	37.2 (36.7-38.2)	37.0 (36.7-38.2)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	11 (19)	4 (24)	
Severe (> 38.5˚C)	12 (21)	3 (18)	
Altered mental status	17 (30)	2 (12)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

The majority of study participants were nutritionally normal (33 placebo, 32 active, including all five treatment failures). Only one child (placebo) was underweight for age; she was HIV positive on highly active anti-retroviral therapy (HAART) for the past 10 months.

Socioeconomic factors of housing, electricity, sanitation, water and maternal education levels were strongly correlated (Table 18). Univariate analysis showed a significant difference in that four (80%) treatment failures came from formal housing (Fischer, $P < 0.05$)(Table 12). At Day 3 post-ingestion, a significantly greater proportion of all patients were reported with more severe cough by caregivers with a tertiary education compared to those with less education (χ^2_6 15.863, $P < 0.05$)(Table 19).

Table 18: Correlation of socioeconomic factors

Correlations					
	Water	Electricity	Education	Housing	Sanitation
Water					
Correlation Coefficient	1.000				
Sig. (2-tailed)					
N	73				
Electricity					
Correlation Coefficient	0.389**	1.000			
Sig. (2-tailed)	0.001				
N	72	72			
Education					
Correlation Coefficient	0.280*	0.208	1.000		
Sig. (2-tailed)	0.016	0.080			
N	73	72	74		
Housing					
Correlation Coefficient	0.572**	0.446**	0.377**	1.000	
Sig. (2-tailed)	0.000	0.000	0.001		
N	69	68	69	69	
Sanitation					
Correlation Coefficient	0.315**	0.254*	0.135	0.438**	1.000
Sig. (2-tailed)	0.007	0.034	0.262	0.000	
N	71	70	71	67	71

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

Table 19: Reported cough at Day 3 post-ingestion according to maternal education levels

DAY 3 POST-INGESTION		Maternal education level			*P* value
		< 10 years formal education	**> 10 years formal education**	**Tertiary education**	
COUGH *n* (%)	Absent/resolved	10 (59)	25 (61)	3 (27)	
	Improving	5 (29)	13 (32)	3 (27)	
	Static	2 (12)	1 (2)	2 (18)	<0.05
	Deteriorating	0 (0)	1 (2)	3 (27)	<0.05
Total		17	41*	11	

*****Where values do not add up to the denominator (n = 41), data were not recorded for the missing number

ADDITIONAL ANALYSIS

Concordance of reported symptoms and clinical signs

There were 114 episodes of patient attendance for follow-up. In 89 reviews, patients reported improving or absent symptoms; 88 found clinical agreement and one was clinically worse (treatment failure). Twelve incidents reported static symptoms; 10 were stable and clinically improving and two were clinically worse (treatment failures). Twelve incidents reported deterioration of symptoms; seven were found to be clinically well, three required a beta-2-agonist for lower airway obstruction and thereafter remained well, and two were clinically worse (treatment failures).

Fifteen patients were missing from follow-up at Day 3 post-ingestion (Figure 1). Of those contacted by telephone (n = 10), seven patients attended their appointment at Day 5 post-ingestion and were improving and three patients were available by telephone only and asymptomatic. Five of the 15 missing patients were not contactable at Day 3 post-ingestion. At Day 5 post-ingestion, one patient attended and four patients were only available for telephone interview; all were improving.

Study drug adherence

All caregivers who attended follow-up and those contacted by telephone (Figure 1) confirmed adherence by history or observation. In one patient (active), the bottle was already completed at the first review as the mother was giving 1 tablespoon instead of 1 teaspoon three times a day; another bottle was not dispensed. Another child (placebo) had completed the bottle at first review; the technique was confirmed as correct and another bottle was dispensed. It was assumed that there may have been some spillage of the study drug. A third child (active) was receiving a twice daily dose rather than three times a day; this was corrected at the first follow-up visit.

Additional clinical information

General CXR changes included opacification and bronchial wall thickening. The CXR was normal in 22 (30%) patients, had single or double lobe changes in 14 (19%) patients and extensive (more than 3 lobes) changes in 32 (43%) patients, of which 21 (28%) patients had a predominantly bibasal pattern. There were 2 (3%) further patients with evidence of a viral lower respiratory tract infection only. Further analysis of CXR changes was not performed as this was beyond the scope of the study.

There were 10 patients (eight placebo, two active; one treatment failure) who were apyrexial at initial assessment, but developed a fever during their stay in hospital.

Eight patients (six placebo, two active) required a beta-2-agonist (via nebulisation, MDI or syrup) due to evidence of bronchospasm (wheeze) during the study: three patients (three placebo, one treatment failure) were given a beta-2-agonist at initial presentation, of which one was discharged with a syrup formulation; one child (active) had pre-existing asthma and used his MDI at home between follow-up visits; one child (placebo) had syrup from prior lower airway obstruction and used it before the first follow-up; and three patients (two placebo, one active) had evidence of bronchospasm at follow-up with good response to bronchodilators and were sent home with an MDI or syrup formulation of a beta-2-agonist.

Eighteen patients (nine placebo, nine active, one treatment failure) suffered diarrhoea after ingestion, either during admission or as reported at follow-up; all responded to oral rehydration.

Five patients (one placebo, four active) developed a contact dermatitis after the clothes they were wearing were soaked in kerosene by accidental spillage during ingestion: four to the anterior chest wall with only superficial peeling and one to the cubital fossa requiring attendance at Burns Clinic for dressings and desloughing.

Seven patients attended their primary health care centres between follow-up appointments: one patient (active) attended due to diarrhoea and vomiting and received oral rehydration solution; another patient (placebo) represented the night after discharge with increasing shortness of breath, was given a brief period of oxygen before being sent home and was improving at follow-up; two patients (both placebo) went to update their immunisations; one patient (active) went between Day 3 and 5 post-ingestion to get her tonsils reviewed and was given a penicillin antibiotic; one newly-diagnosed TB patient (placebo) went to enrol at her

local TB clinic; the seventh patient (active) was an inpatient at Day 3 post-ingestion awaiting a second gastric washing as part of her TB workup.

HIV investigation (six placebo, five active, three treatment failures) was done as indicated during the study; all patient's results were negative. Of the 20 HIV-exposed patients (13 placebo, seven active), four mothers were currently on HAART, 12 were not, and details were not obtained on another four. There was only one HIV positive child (placebo); she was already on HAART.

Chapter Three

DISCUSSION

The double-blind randomised controlled trial allowed for comparable placebo and active treatment groups from which conclusions could be drawn, although the study numbers are small. Both groups presented with varying degrees of pneumonitis as reflected in the severity of presenting respiratory findings, fever and altered mental status. The small proportion of treatment failures suggests that in children secondary infection is rare in kerosene-associated pneumonitis after ingestion. The lack of a significant difference in the number of failures between placebo and active groups argues against the efficacy of prophylactic antibiotics in children with mild to moderate respiratory disease. This is supported by the similar length of hospital stay for both groups, and minor differences in reported cough and temperature at Day 5 post-ingestion. For many patients, the presence of symptoms and signs at both follow-up visits can be explained by the natural history of the pathological process as described in animals. Animal studies reported an alveolitis peaking at 3 days post-ingestion and resolving by 10 days and alveolar proliferation and thickening peaking at 10 days and resolving by 2 weeks (20, 21, 22, 24, 34). Confounding conditions such as URTI or active TB disease are another explanation. Therefore, the persistence of symptoms and signs in placebo and active groups may plausibly be a reflection of the ongoing inflammatory process of kerosene-associated pneumonitis or a confounding condition and not due to secondary bacterial infection. This casts further doubt on the impact of any treatment received. The results of the study are consistent with the null hypothesis that prophylactic antibiotics neither improve the outcome of children with kerosene-associated pneumonitis following ingestion nor hasten clinical resolution in the studied population.

The lack of differences in presentation between the outcome groups of treatment failure and success suggest that there are no reliable clinical parameters that predict those patients who may deteriorate after discharge. Simmank et al (13) demonstrated that children with kerosene pneumonitis following ingestion showed no increased respiratory morbidity in the 3 months following ingestion and this was true for all severities at initial presentation. The updated 2011 British Thoracic Society (BTS) guidelines (41) on the management of community acquired pneumonia (CAP) suggest certain clinical severity indicators for infants and older children to determine which patients should receive hospital-based care. However, they also state that “there is no single validated severity scoring system” and that the ultimate decision to refer children with CAP for hospital admission is based on a number of clinical and social

findings. Similar principles may apply to decisions on the management of children with kerosene-associated pneumonitis. Some patients in our study had initial clinical findings within the severe category, had the BTS guideline criteria been adopted, but were successfully managed as outpatients. It seems that initial clinical measurements are probably best reserved for use in the triage setting to determine referral criteria only (39) and cannot reliably predict those who may deteriorate once discharged.

Patients in our study who did deteriorate once discharged and required a change to their treatment regimen, namely treatment failures, were compared with treatment successes based on an assessment of reported symptoms and clinical signs at follow-up. Study rigor demands that the measures, used to determine treatment failure, are defined. But these definitions can create problems. Firstly, specific cut-off values for continuous variables used to define the presence or absence of an outcome measure may result in the inclusion or exclusion of patients, impacting on true estimates of outcome. This factor is reiterated in a Pakistan study on the use of standard versus double-dose cotrimoxazole for the treatment of childhood pneumonia (46). Although they classified treatment failures as any patient whose condition remained unchanged on Day 2, one of the determinants of improvement was a RR that was either normal for age or more than 5 breaths per minute (bpm) lower than at initial assessment. The authors comment on the sensitive nature of the definition of treatment failure and that perhaps a reduction in RR of only 3bpm would have created less treatment failures. They reported that out of a group of children (n = 103) who should have had their drug changed according to their respiratory criteria but did not, 85% recovered. Secondly, continuous variables may lose clinical relevance when categorised. This was seen in our study when significant differences in RR or recorded temperatures were not similarly significant for tachypnoea or fever or severities thereof. And thirdly, many signs are altered by other factors. For example, an anxious child who is irritable will have a raised RR and heart rate, but these may settle over time as the anxiety decreases.

Given these concerns on study variables and definitions, the differences between treatment failure and success in reported symptoms and clinical findings at follow-up on Day 3 post-ingestion may be interpreted in two ways. On one hand, the significant differences in cough, shortness of breath, RR severity, flaring, grunting and crepitations are expected, because they are clinical manifestations of the pathological process on which the diagnosis of treatment failure or success rest. Alternatively, the absence of differences in certain other symptoms and signs did not detract from the assessment of whether a patient was a treatment success or failure. In summary, determination of outcome cannot be based exclusively on the presence of absence of one particular symptom or sign. Rasmussen et al's (46) mention of

the WHO Acute Respiratory Illness guidelines for improvement as "slower breathing, less fever, eating better" concurs.

The only risk factor for treatment failure was residence in formal housing. This is surprising as suburbs within the RCWMCH drainage area, where most kerosene cases occurred, are a mixture of low-cost housing and informal shacks reflecting peri-urban communities with low socioeconomic status (47, 48), a known risk factor for kerosene ingestion. However, our study's applied definition of formal housing as a brick structure is very broad and associated factors such as overcrowding, water availability, sanitation and electricity are independent of the housing structure. Therefore, the housing difference between treatment failure and success should not be taken at face value; more in-depth data on overall socioeconomic features needs to be collected to draw appropriate conclusions.

A number of factors were analysed to try and identify potential confounding conditions or risk factors, if not for treatment failure then for persistence of symptoms and signs. The presence or absence of these factors was similar in both placebo and active and treatment success and failure groups.

The differences in clinical presentation between those with a preceding URTI and those without show a smaller proportion of patients with an URTI vomiting post-ingestion. However, those with a preceding URTI were more likely to be flaring, although the RR was similar between groups. Flaring is a centrally mediated sign and is a measure of an increased respiratory drive. Perhaps a blocked nose due to the URTI had already primed this response. The differences in recorded temperatures at Day 3 post-ingestion, but not fever or temperature severity reflect the nuances of interpretation of continuous variables which have more applicability in the clinical context when categorised. At Day 5 post-ingestion, the increased reporting of fever is expected in the group with new-onset URTI. Although a common finding, the presence of an URTI did not seem to have an impact on overall outcome and in fact provided an alternative explanation at follow-up for the presence of symptoms such as cough and fever and clinical findings of fever. This is similar to the USA Co-operative Kerosene Poisoning Study (26) in which the prevalence of URTI within the studied group was not unusual and there was "no uniform relationship to the presence or absence of pulmonary complications".

South Africa has one of the world's highest TB burdens. Figures from 2010 show an incidence of 981 per 100 000 people in a population of 50 million (49). The City of Cape Town reflects this burden with 2010 incidence figures of 800 per 100 000 people (50). In certain areas from which our study population was drawn, the mean annual risk of TB infection for children was 4.1% (51). 2009 figures report the notification of new cases under

15 years as 664 to 1044 per 100 000 people (52). Three of our study participants were diagnosed with active TB disease, which is very likely representative of the TB status of children with kerosene ingestion presenting to RCWMCH. The greater proportion of children with active TB disease reporting static or deteriorating symptoms at first follow-up may have been due to an increased awareness by caregivers subsequent to the diagnosis of TB. The numbers are too small to show the true impact of active TB infection, but do show that in the studied population, TB may be more common than the need for antibiotics in children with kerosene-associated pneumonitis.

Vomiting is deemed a risk factor for aspiration, which in turn is the cause of pneumonitis following kerosene ingestion. However, there seems to be lack of agreement on the impact of vomiting on the development of pneumonitis. The USA Co-operative Kerosene Poisoning Study (26) stated that pulmonary complications and central nervous system manifestations were seen more frequently in patients who vomited post-ingestion. Four studies, which evaluated patients with a history of kerosene ingestion, commented on a relationship between vomiting and the development of pneumonitis. Lifshitz et al (53) showed a statistically significant correlation between vomiting and pneumonia and Lucas (54) stated that 85% of children who developed a pneumonitis post-ingestion had vomited. However, Gupta P et al (55) showed no difference in clinical symptoms and radiological extent of lung involvement with regards to vomiting post-ingestion and Dudin et al (28) showed no statistically significant relationship between vomiting, respiratory distress and respiratory severity for those who were distressed. Another study (13), which looked at illness severity and outcome prediction, found no increase in morbidity in those patients who vomited post-ingestion. All patients in our study were assumed to have aspirated as the presence of symptoms and/or signs suggestive of pneumonitis were necessary for inclusion. The lack of differences in clinical presentation and symptoms and signs at follow-up suggest that for those with pneumonitis, vomiting post-ingestion had no impact on either the severity or subsequent outcome. However, to be able to investigate the impact of vomiting on the development of pneumonitis, all patients with a history of kerosene ingestion, including those who were asymptomatic, would need to be included.

The USA Co-operative Kerosene Poisoning Study (26) states that children under 18 months are at risk of developing pulmonary complications following kerosene ingestion. In our study population, the only impact of age was that a greater proportion of children less than 2 years of age had a raised RR with greater severity at presentation. Although a younger age group had a more severe respiratory presentation, both severity and young age did not affect outcome. All patients in our study were over 12 months, so we cannot comment on the outcome of kerosene pneumonitis in infants. To be able to determine the risk of pulmonary

complications in younger children, a comparison of symptoms and signs in all children who ingested kerosene by age group would be needed.

Other potential risk factors identified prior to the start of the study, did not increase the risk of treatment failure or persistence of symptoms and signs. The differences in patients with a smoking contact only reflect the lack of clinical value that continuous data can have when not categorised. HIV-exposed but uninfected infants are more susceptible than HIV-unexposed infants to the development of severe infections or pneumonia due to opportunistic infections (56, 57, 58). Although the study did not enrol any infants, HIV exposure did not seem to be a risk factor for deterioration for children older than 12 months as none of the treatment failures were HIV exposed. The differences between the finding of crepitations at presentation and follow-up and RR at follow-up according to HIV exposure status are not likely to have any clinical relevance. To explore the effects of HIV exposure and infection on kerosene pneumonitis, one would need a larger sample size with more HIV-infected children. The small number of patients with a prior respiratory history showed no increased susceptibility to treatment failure or persistence of symptoms and signs. It was expected that patients with a prior respiratory history may present with a more severe pneumonitis initially, but this was not reflected in the results as those without a prior respiratory history were more inclined to be flaring and have increased RR severity. Perhaps the respiratory-naive patients had a more marked inflammatory response with appropriate respiratory compensation.

Malnutrition would be expected to deliver worse outcomes in children with kerosene-associated pneumonitis. Gupta P et al (55) reported all three fatalities in patients with severe malnutrition (weight-for-age below 60% of expected values): one died due to myocarditis and two due to respiratory failure. They also showed that severe malnutrition was associated with more extensive radiological involvement. A recent survey from India (6) reported that male gender and malnutrition (weight-for-age below 80% of expected values) were significantly associated with prolonged hospital stay. Although our weight measurements are a once-off value in time and as such not an accurate reflection of the long-term nutritional status of a child, the lack of study participants with malnutrition precluded adequate interpretation of its impact on outcome.

Socioeconomic factors may be expected to impact on outcome. Risk factors for kerosene exposure (59, 60) and unintentional childhood poisoning (8, 9) such as storage in juice bottles were not found to have an impact on outcome in the studied population. The greater proportion of all patients with static or deteriorating cough at Day 3 post-ingestion according to a higher education level possibly indicates that parents with better education are more

likely to exaggerate the severity of reported symptoms. In general, the range of caregiver education levels did not impact on the accuracy of assessment of patient progress. In those treatment successes where caregivers reported deterioration in symptoms, either a new-onset URTI or bronchospasm explained such deterioration and the assessment remained that the child was improving. In opposition to this, in only one treatment failure did the caregiver report improving symptoms where the clinical examination revealed deterioration. Therefore, a greater proportion of reported deteriorating symptoms resulted in a clinical assessment of treatment success rather than the more detrimental outcome of a parent believing their child was improving when in fact he/she was not.

Our study was concluded before the proposed sample size was achieved. When considering early stopping of a study it is important to consider issues of harm over and above any treatment effect (61). In this study, potential issues of harm would be deaths, withholding treatment from patients who may need it, significant numbers of treatment failures not responding to altered regimens and adverse effects of treatment.

If one takes the children with respiratory distress and therefore confirmed pneumonitis on presentation in the Reed and Conradie (23) study (n = 53), and add them to our placebo group, there are 88 patients who did not receive antibiotics. Within this group, there is one death (1%, from Reed and Conradie), three treatment failures (3%, from this study) and 84 (95%) who recovered without antimicrobials. Considering patients presenting to RCWMCH from 2003 until May 2012, including study participants, there have been 1056 patients with kerosene ingestion; there have been two deaths (0.2%)(unpublished data from RCWMCH PIC Clinical Poisonings Database). It is not known which patients received antibiotics, but the low mortality is reassuring. About 15% of the 1056 patients would not have been eligible for this study as some were too ill (n = 27; 2.6%) and others asymptomatic (n = 131; 12%).

The potential for withholding treatment from patients who may need it was dealt with in the study design. Strict exclusion criteria meant that children too sick and those requiring an antibiotic for another reason were not included. The primary outcome measure, treatment failure, was defined to ensure as far as possible that all children showing deterioration and therefore having suspected secondary bacterial infection were detected timeously and their treatment regimen changed accordingly. Where indicated, those on placebo were started on an antibiotic and those already receiving active treatment had their antibiotic changed. In addition, the existing evidence, although limited, casts doubt on the efficacy of antibiotics and therefore withholding treatment was not considered as potentially harmful to patients.

The lack of differences in treatment failures between placebo and active groups is an indication that future withholding of antibiotics from children with mild to moderate

pneumonitis following kerosene ingestion is not harmful. In a study with rare treatment outcomes, risk ratios approximate odds ratios. A relative risk of 0.60 (95% CI, 0.11 to 3.37) is a relative risk reduction of 0.40 (95% CI, -2.37 to 0.89), meaning that amoxicillin reduced the risk of treatment failure by 40%. This is in reality a 4% absolute risk reduction, which is based on one additional failure in the placebo group. Further analysis of treatment failures affirms that antibiotics may be withheld in the group of patients studied. A lack of homogeneity in pneumonitis severity within both the treatment (placebo versus active) and outcome (failure versus success) groups was explored, but there were no significant differences found. Therefore, the risk of treatment failure remains constant irrespective of severity at presentation. Treatment failures were easily identifiable. They all presented within 3 days post-ingestion. Treatment failures showed improvement once their regimen was changed. Four were improving at follow-up and the fifth, who was lost to follow-up, was identified by the mother on reported symptoms and had a new-onset URTI which may have explained the deterioration. Additional factors such as active TB disease, asthma co-morbidity and new-onset URTI offered comprehensible alternatives to secondary bacterial infection for patient deterioration in the treatment failures. Moreover, it is possible the natural disease process of kerosene pneumonitis was the reason for apparent deterioration at Day 3 post-ingestion, but the study was not designed to assess if these treatment failures may have recovered without recourse to antimicrobial therapy. Further analysis of the large proportion of treatment successes in the placebo and active groups showed only minor differences in reported symptoms and clinical signs at follow-up. The natural course of the disease is spontaneous improvement and ultimately resolution, in a time period beyond the scope of the study.

The final issue of potential harm in stopping our study early would be adverse treatment effects. As amoxicillin is a common antibiotic registered for the treatment of secondary infection there were no such concerns. However the costs of unnecessary antibiotic use and risks of developing resistance are worrying. If one assumes a 95% treatment success rate without antibiotics and 2.6% of kerosene admissions to RCWMCH to be too sick to be excluded from receiving an antibiotic and applies these figures to an estimated 50 000 kerosene poisonings in South Africa (18), then every year, about 46 000 unnecessary courses of antibiotics are given to children who have ingested kerosene. This equates to a cost of R142 140 per annum using the study drug cost of R3.09 per bottle.

These points provide the rationale for early truncation of the study. The lack of harm to patients, the money spent on ongoing study costs and the inconvenience to patients are some of the reasons justifying a truncated study. The ethics of ongoing participant enrolment with no apparent benefit due to the rarity of secondary infection following kerosene pneumonitis

and the potential for inducing antibiotic resistance with inappropriate use were also factors in this decision.

The need for reassessment in all patients is important to consider. For all medical conditions, children are discharged from hospital when they no longer require specific nursing care or repeated assessment by a doctor and they can be entrusted back to the caregivers for continued care. The decision to discharge or not admit can only be considered if a child is stable or improving, caregivers have a full understanding of how to give any treatment prescribed, information is given on symptoms and signs which may indicate deterioration, and there is either an arranged follow-up appointment or the caregiver has accessible medical facilities should the child need reassessment. The BTS guidelines for CAP (41) suggest that for children treated in the community, caregivers should be given advice on management and identifying signs of deterioration and other serious illness. They must also have a "safety net" for further assessment, which is in the form of knowledge on how to access health care, an arranged follow-up appointment or prior discussion with other healthcare providers to ensure a patient has access to reassessment should it be required.

This "safety net" is especially important when antibiotic prophylaxis is not given, as our study results suggest. If patients with mild to moderate pneumonitis following kerosene ingestion can be reassessed within the time period for possible deterioration, within 3 days post-ingestion, then antibiotics can safely be withheld. If follow-up is not possible, the value of antibiotic prophylaxis must be reconsidered. This decision is dependent on the reason for not being able to attend follow-up, as in many circumstances an alternative plan can be made. If the doctor is unavailable, then another healthcare provider can be appointed. If a caregiver is unable to attend due to prior commitments, an appointment can be scheduled accordingly. If a caregiver cannot afford to attend the treating medical facility, the child can be handed-over to medical staff at a closer site. In some instances, particularly in developing countries, patients live in rural areas far from medical help and in these instances it might be reasonable to keep the child in hospital until the time period for potential deterioration has passed; this depends on other practicalities such as number of hospital beds, parent willingness etc. If it is not possible to communicate with the caregiver due to language barriers, then an interpreter should be sought. If adequate communication is not possible, then the ability to inform the caregiver on how to give medication is questionable leaving any value of antibiotic prophylaxis in doubt. The level of caregiver education should not be a factor, as previously discussed. Bearing in mind the results of our study, specifically the small number of treatment failures, lack of treatment effect and the majority of caregivers accurately assessing their child's progress, it may be reasonable to continue withholding antibiotic prophylaxis in those patients where the reason for the inability to attend follow-up

cannot be overcome. This decision must be tailored according to the circumstances for each individual patient with the proviso that all caregivers have a good understanding of symptoms and signs suggestive of deterioration and can access local medical facilities if necessary.

Limitations

The results of our study are limited by the overall small sample size. Detractors will make the point that the study was concluded too early, thereby limiting the number of treatment failures on which the argument for or against prophylactic antibiotics could be made. Is there really no difference in outcome between placebo and active groups or is the sample size too small to show any differences as only large differences between groups will be detected?

The initial protocol design aimed to enrol 200 patients over a 2-year period, based on previous admissions to RCWMCH. As there were no prior RCTs investigating the efficacy of prophylactic antibiotics in kerosene-associated pneumonitis in children, the lack of prior treatment failure proportions meant we could not accurately calculate a required sample size. The figures of suspected secondary infection (15 to 49%) from two prior studies (23, 36) were equated to potential treatment failures and a mid-way point of 25% arbitrarily chosen. Patient recruitment was slower than expected and the accrual of the study's outcome event (treatment failure), even slower. In studies where there is apparent benefit with a specific treatment, early stopping may overestimate the observed benefit. Predefined statistical stopping rules with very low significance levels can help (61), but it is suggested that there should be a minimum of 200 outcome events before considering stopping (62). However, in this study the small number of outcome events and lack of treatment differences (and no prior RCTs with which to compare our results) made the possibility of any significant differences with the proposed sample size very unlikely. This reason for stopping a study early is termed "futility" and argues that "continuing the trial may not be justifiable in terms of time, money and effort" (61). Using the study's final numbers (n = 74) and risk of treatment failure (overall risk 7%, placebo 9% and active 5%), a level of significance of α = 0.05 and power 0.80, one would need a minimum of 638 participants in each treatment group to adequately accept or reject the null hypothesis. At the rate of recruitment (74 patients in 14 months), this would mean a period of 16 years to get a sufficient sample size.

The lack of follow-up attendance by participants further reduced the numbers available for clinical re-evaluation and may have led to an underestimate of the true occurrence of clinical signs. However, our study showed good concordance between reported symptoms and clinical signs for both the patients who attended the first follow-up and those who reported improving symptoms via telephone interview at Day 3 post-ingestion and were clinically well at attendance on Day 5 review. Therefore, we can assume that telephone interviewees were indeed improving and not missed treatment failures.

Most patients were referred from surrounding Day Hospitals and clinics and therefore presentation at RCWMCH was dependent on the availability of ambulances for transport.

Once at RCWMCH, patients are placed in a queue with other emergency patients to be seen by the on-duty doctors. Therefore the clinical findings at presentation were taken at different times post-ingestion. Due to the study being a RCT, the time post-ingestion for both treatment groups was equal and therefore comparable.

RECOMMENDATIONS

Based on the findings from this population of patients and supported by both the Pakistan study (46) and BTS CAP guidelines (41), the following recommendations apply:

1. Children with mild to moderate kerosene-associated pneumonitis DO NOT require routine prophylactic antibiotics.
2. Follow-up, preferably within 3 days post-ingestion, is advised.

There are several areas that require future study. A better way of investigating risk factors for deterioration would be to recruit all patients with a history of kerosene ingestion, irrespective of severity of illness, allowing for an increased sample size. As so few patients deteriorate, most patients could safely be discharged without antibiotics, with a routine follow-up at Day 3 post-ingestion for all patients. This would alleviate the inconvenience to patients of two appointments, but still allow for detection of deteriorating patients and collection of information. Most failures can be expected to present within this time period. It would also be helpful in assessing if routine follow-up is necessary when antibiotics are omitted. If there are indeed so few deteriorating patients, one may be able to place the responsibility on the caregiver for detecting deterioration. A future area for study is the need for antibiotics in severely ill patients or those at high risk for progression to secondary bacterial infection, such as HIV-infected or malnourished patients.

CONCLUSION

Despite the small sample size, there are conclusions that can safely be drawn from these data, which are generalisable to children with mild to moderate respiratory disease after kerosene ingestion. The small number of treatment failures supports the view that secondary infection following kerosene-associated pneumonitis in children is rare. The number of treatment successes and the lack of differences between placebo and active groups show that antibiotic prophylaxis does not improve outcome. There is no evidence to support their continued use. However, as there are no predictive risk factors for deterioration, the omission of antibiotics in the management of these patients does not obviate the need for routine reassessment by a medical practitioner, preferably at Day 3 post-ingestion.

APPENDICES

Appendix A
Research Protocol
STUDY: The efficacy of prophylactic antibiotics in the management of pneumonitis following paraffin ingestion in children

PRINCIPAL INVESTIGATOR:
Dr Kate Balme
Poisons Information Centre, Red Cross Children's Hospital
University of Cape Town, Cape Town, South Africa
Email: kh.balme@uct.ac.za
Tel: 021 658 5308
Fax: 021 658 5331

CO-INVESTIGATORS:
Prof Heather Zar
Department of Paediatrics and Child Health, Red Cross Children's Hospital
University of Cape Town, Cape Town, South Africa

Prof Mike Mann
Poisons Information Centre, Red Cross Children's Hospital
University of Cape Town, Cape Town, South Africa

PROPOSED DATES OF STUDY – March 2010-December 2011

PLACE OF STUDY: Red Cross Children's Hospital, University of Cape Town, Cape Town, South Africa

Background

In the developing world, paraffin (kerosene) ingestion accounts for a large number of visits to healthcare facilities, especially amongst children [1, 4, 5, 6, 7, 8]. At Red Cross War Memorial Children's Hospital, for each of the past six years (2003-2008), paraffin ingestion presentations have been on average 100 patients per annum, over 20% of all poisoning cases seen.

After ingestion of paraffin, inhaled vapours and aspiration of liquid hydrocarbons commonly lead to a chemical pneumonitis. The management is supportive, assisting with oxygenation and ventilation and the majority of patients completely recover.

Pneumonitis following paraffin ingestion is initially a sterile chemical injury. The inflammatory response results in respiratory difficulty and hypoxia, fever and a raised white cell count [10]. Chemical pneumonitis reportedly occurs in 12-40% of ingestions [17 – SAMF] and in hospital studies of patient admissions, between 54-80% had respiratory symptoms [5, 14, 21]. Such chemical insults are thought to render the lung tissue more susceptible to superimposed bacterial infection. A possible mechanism for this is disruption of the alveolar surface, leading to altered bacterial clearance and subsequent overgrowth [16]. Because objective findings such as fever, tachypnoea and raised white cell count occur with both paraffin-associated pneumonitis and pneumonia, it is difficult to distinguish between the two, and know when to initiate antibiotic therapy. In South Africa, prophylactic antibiotic use is common because of the high burden of malnutrition, HIV and TB and the assumption that these immunocompromised children are more at risk of superinfection. In the past, the practice at Red Cross Children's Hospital was to give all patients with suspected pneumonitis following paraffin ingestion prophylactic antibiotics.

Animal studies have looked at both bacterial superinfection and antibiotic use. Histological samples from baboons injected with intratracheal paraffin showed no organisms or positive lung cultures as compared to controls, refuting the occurrence of secondary bacterial infection [11]. In another study, lung cultures performed on specimens from guinea pigs given intragastric paraffin, showed no difference in bacterial recovery rates between controls, those with untreated paraffin pneumonitis and those treated with either procaine penicillin, ampicillin or cephalothin [16]. Furthermore, dogs given intratracheal median lethal doses of kerosene receiving either dexamethasone and ampicillin or nothing, showed no significant difference in mortality or in clinical, radiological and pathological findings [15].

A study done on rural South African children assessed secondary infection with paraffin-associated pneumonitis [Reed and Conradie 1997]. Fever and respiratory distress on day 1 suggested bacterial infection, at which time blood cultures and chest X-rays were performed. 50% of patients fulfilled these criteria, but only 3.7% had a positive blood culture. If symptoms were present at day 4, the same investigations were done in view of possible nosocomial infections. Of this group, 6% had positive blood cultures. There is no comment as to how many children had blood cultures on both days. Only one child was given antibiotics. She presented after seven days with ongoing fevers, respiratory distress and pneumatocoeles on chest Xray. None of the remaining children received antibiotics and those with positive cultures recovered within a similar period as those with negative cultures,

with no recourse to therapeutic antibiotics. The authors comment that most children will recover with antipyretics and oxygen therapy, and that secondary infection is rare [14].

To date, there is only one human trial, which analyses the efficacy of antibiotics [Singh et al, Libya 1992]. Four treatment groups, of 20 subjects each, received: Ampicillin and Metronidazole (Group A), Carbenicillin (Group B), Ampicillin (Group C) or Metronidazole (Group D). A fifth group, which authors termed a control group, received no antibiotics for 48 hours, but if they became symptomatic during this observation period, they were given antibiotics as per Group A. Improvement was assessed clinically (resolution of fever, tachypnoea and chest rales) and radiologically. Of the treatment groups, mean time for clinical recovery was 5-7 days. Although Group A seemed to recover slightly quicker, analysis of variance showed no statistically significant difference between the four treatment groups. Of the control group, nine of 20 children were symptomatic at 48 hours and given antibiotics. All nine remained symptomatic on Day 8. The number of patients with radiological deterioration as assessed at Day 8 for Groups A to D was 2(10%), 3(15%), 3(15%) and 7(35%), respectively. The control group had 7(35%) with radiological deterioration, all of whom were also symptomatic and received antibiotics. Singh et al suggest an unsatisfactory response to delayed treatment in symptomatic patients, despite no statistical comparison of the control and treatment groups.

These studies cast doubt on the use of prophylactic antibiotics in the management of paraffin-associated pneumonitis. However, there is currently no consistent agreement on whether prophylactic antibiotics are of benefit and therefore wide variability in practice globally. Therefore, this study will investigate the use of prophylactic antibiotics to provide sufficient evidence to either recommend or discourage their use.

Feasibility of project and importance of problem

The 2008 WHO/UNICEF 'World report on child injury protection' declares poisoning as one of the five most important causes of unintentional injury deaths, behind road traffic injuries, drowning, falls and fire-related burns. Poisoning amounts to 4% of injury deaths between the ages of 0-17 years and accounts for 11% of all unintentional injuries in children below 15 years [9]. At Red Cross War Memorial Children's Hospital, poisoning constitutes 8% of all medical admissions.

Industrialised countries show the most frequently ingested substances to be household products, medications and drugs [2, 3, 9], whereas in developing countries, they are more commonly household agents, pesticides, poisonous plants and animal or insect bites [2, 9]. Regional hospital studies record paraffin (kerosene) as the leading cause of acute childhood poisoning: in India 47% [1, 4, 6], South Africa 78% [5, 18] and Kenya 60%. In middle and low-income groups, hydrocarbon ingestion is the most common agent involved in childhood poisoning, particularly between the ages of 1 and 3 years [9].

Matzopoulos and Carolissen (South Africa 2006) state that accurate national data on morbidity and mortality associated with paraffin poisonings in developing countries is not readily available, as surveillance systems are non-existent. Figures taken from South African hospital statistics grossly underestimate the incidence: only 50% attend the clinics, cases are recorded by their diagnosis and not cause of injury, and fatalities are often not recorded as unnatural deaths. Recent South African figures, extrapolated from data on paraffin usage and

hospitalisations per million litres sold, estimate the incidence of childhood paraffin ingestion at 40 000 – 60 000 cases annually [17].

Aim

To determine the efficacy of prophylactic antibiotics in the management of paraffin-associated pneumonitis.

Objectives

Primary objectives:

To investigate whether the use of prophylactic antibiotics affects the clinical course of children with pneumonitis following paraffin ingestion

Secondary objectives:

To report the main clinical parameters associated with pneumonitis and paraffin ingestion

To identify risk factors for the development of pneumonitis following paraffin ingestion

Study design

A double-blind placebo-controlled trial of prophylactic antibiotics in the management of paraffin-associated pneumonitis following ingestion will be performed

Study population

Children older than 3 months, attending Red Cross Children's Hospital MOPD/Emergency department, with respiratory symptoms (cough or difficulty breathing) or signs (*age specific tachypnoea, chest indrawing, stridor, wheezing or crepitations) after suspected or known paraffin ingestion, will be eligible for inclusion.

Inclusion criteria:

- ingestion in the preceding 24 hours
- presence of respiratory symptoms and signs at presentation (see definition of terms)
- Informed consent obtained from parent or legal guardian
- Resident within the Red Cross Hospital drainage area and able to come for 2 follow-up appointments

Exclusion criteria:

- Too ill to be excluded from receiving antibiotics ie requiring more than 2L nasal prong oxygen (FiO2 40%), CPAP or ventilation or requiring High Care or ICU admission
- Allergic to Amoxicillin

Age specific tachypnoea will be regarded as:

Respiratory rate >50 breaths per minute (2 to 12 months) or

Respiratory rate >40 breaths per minute (12 months to 5 years)

Methods

A study researcher will screen sequential children with known or suspected paraffin ingestion. Informed consent will be available in 1 of the three official languages – English, Afrikaans or Xhosa (Appendix D). Eligible children who meet the inclusion criteria will be randomised to receive either placebo or Amoxicillin.

All children will undergo a history and examination by the admitting doctor (see Appendix A1) as is standard practice. In addition, a study researcher will perform a more detailed history and examination after enrolment to obtain any missing information (see Appendix A2). All children will have pulse oximetry measured in room air. A chest Xray will be performed on all children, at least 6 hours post-ingestion, as is usual practice. The X-rays will be reported according to a standard format by a radiologist. Additional tests, including blood tests, will be done at the discretion of the admitting doctor and according to clinical indications. Treatment will be given as clinically indicated.

Study regimen, treatment allocation and blinding

All children will be randomised to receive either placebo or Amoxicillin syrup at a dose of 20-30mg/kg/dose 8 hourly for 5 days.

A placebo will be manufactured by the Red Cross Hospital Pharmacy to have an identical appearance and similar taste to Amoxicillin. The dispensing pharmacy will not be blinded.

The allocation schedule for treatment will be constructed using computer generated random number tables. The allocation sequence will be presented to the study investigator on a monthly basis, by means of sequentially numbered opaque sealed envelopes. Professor Mike Mann will hold the code to the treatment allocations and be consulted if they need to be broken.

Follow-up

All patients enrolled in the study will have two follow-ups, at 72 hours and 5 days post-ingestion, during which they will be assessed for symptoms, signs and adherence (see Appendix B and C)

Children who do not return for their appointments will be phoned and a telephone interview conducted with the mother about symptoms. Three attempts will be made to contact these patients, and if unsuccessful, they will be excluded from the study.

If a child is seriously ill, deteriorating or not improving as expected, the code for the treatment schedule will be broken and the child managed appropriately. These cases will be regarded as treatment failures.

Outcome measures

The length of stay in hospital for medical reasons (number of days) and the presence of respiratory symptoms and signs at 72 hours and 5 days post ingestion will be used as the study's outcome measures.

Sample size and duration

The intended study time is March 2010 to December 2011, during which a sample of approximately 200 patients is anticipated, based on previous admissions at Red Cross War Memorial Children's Hospital. If there is shown to be no difference between the two treatment groups, it implies that there are many children receiving antibiotics unnecessarily. Subsets of the patients will be analysed within the groups, to try to identify factors associated with differences in outcome.

Validity and reliability of instruments

Monitors, laboratory analysis and radiology will be as per standard management of any child attending the hospital with a pneumonitis or pneumonia.

Analysis and statistical software

The faculty statistician who is available to advise researchers in the Department of Paediatrics and School of Child and Adolescent Health will be consulted.

Ethics

The trial will be conducted in accordance with the Declaration of Helsinki 2008. Written, informed consent will be obtained from a parent or guardian. Permission to conduct this study has been granted by the Head of Paediatric Emergency Medicine and all relevant consultant specialists.

The protocol will be submitted to the Research Committee of the Institute of Child Health, Red Cross Children's Hospital and the Ethics Committee of the Faculty of Health Sciences, University of Cape Town, South Africa.

Budget

Item	Cost per unit	Units required	Total Cost
Placebo Amoxicillin 250mg/5ml (100mls)	R3.09 R3.09	100 bottles 100 bottles	R309.00 R309.00
Stationary/binding/printing	R5 000.00		R5 000.00
Telephone calls	R10.00	50	R500.00
Patient transport (2 return taxi fares)	R80.00	200	R16 000.00
Miscellaneous	R5 000.00		R5 000.00
TOTAL			**R27 118.00**

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Appendix B1
PATIENT INFORMATION AND CONSENT FORM

"The use of prophylactic antibiotics in the management of pneumonitis following paraffin ingestion"

You and your child are requested to participate in a medical research study done at Red Cross Children's Hospital. The following information will describe the study and your child's role as a participant. Please read carefully and feel free to ask questions.

Background and reason for study
Your child has been hospitalised because he/she drank paraffin. The paraffin can be breathed in when initially drank, or the liquid might come up from the stomach, especially if he/she vomits, and go into the lungs. This causes irritation in the lungs, and can lead to fever, sleepiness, fast breathing and maybe even a tight chest.
We know that paraffin can cause irritation of the lungs, but we are not sure if it causes infection. If it does cause infection we would use an antibiotic, but other studies have shown that there is no difference in improvement between those given an antibiotic and those not. The current practice at Red Cross Hospital is not to give an antibiotic to children after drinking paraffin. From this study, we hope to learn if children who are given an antibiotic get better quicker.

How will the study be done?
A doctor will do a thorough examination of your child.
Your child will have his/her temperature, heart rate, breathing rate and blood oxygen level recorded regularly during admission.

He/she will be given a medicine bottle, which contains either a real antibiotic or a mixture that looks and tastes the same, but has no antibiotic (this is called a placebo). Neither you nor the doctor will know which type of bottle your child has received.
Depending on how much paraffin went into your child's lungs, we expect him/her to get better over the next 6 to 72 hours. If he/she does not get better, he/she will be seen by one of the doctors who knows what is in each medicine bottle and will be treated appropriately.
It is very important that you do not use this medication for anyone else in your home.

Any additional treatment, such as oxygen, panado and nebulisation, will be given as needed. Your child may need a blood test, which can be done by a finger prick. This tests for any evidence of infection. A chest Xray will be done on your child during his/her admission, which is a routine investigation for children admitted after drinking paraffin.

After discharge, your child will need to come back for 2 appointments within the first week. He/she will be re-examined and you can tell us about his/her progress and symptoms. The cost of transport for these repeat visits will be covered by the research study and the appointment will be at a time, which is convenient to both you, your child and the doctor. You will not have to wait in the regular patient queue to be seen, but will be seen immediately.

What does the study mean for you and your child?
Your child will be treated in the same way as any child with paraffin ingestion.
There are no major side effects from the treatment. The antibiotic is commonly used for your child's condition, and for many other children with different chest infections.
There are studies showing no difference between giving an antibiotic after paraffin ingestion and not giving an antibiotic, so there is no danger if your child receives a placebo.

The benefit to your child will be to receive adequate treatment and follow up during his/her illness. This study will benefit future children with breathing difficulty after paraffin ingestion, because it will help us to know whether antibiotics make any difference to getting better.

Confidentiality
Your child's study records will be kept confidential. Neither you nor your child's name will appear in any publication that may arise from this study.

Voluntary participation
You may choose for your child to participate in this study. You may also choose not to be a part of this study and this will not affect any treatment that your child will receive.

I have read and understood this form. My questions have been answered. I voluntarily consent to allow my child to participate in this study.

I, _____, the parent/legal guardian of

_____ agree to allow him/her to participate

in this study.

Signed: _____ Witness: _____

Date: _____ Date: _____

Patient sticker:

Appendix B2
(AFRIKAANS)
PASIENT INFORMASIE EN TOESTEMMINGSVORM

"Die gebruik van profilaktiese antibiotika in die behandeling van pneumonitis na die inname van paraffien"

U en u kind word versoek om deel te neem aan 'n mediese navorsingstudie by Rooi Kruis Kinderhospitaal. Die informasie wat hier volg sal die studie self asook u kind se rol as deelnemer beskryf. Lees asseblief noukeurig verder en vra gerus enige vrae.

Agtergrond en rede vir die studie.
U kind is in die hospital omdat hy/sy paraffien gedrink het. Paraffien kan ingeasem word wanneer dit gedrink word, of die vloeistof kan opkom vanaf die maag en die longe binnegaan (veral as u kind opgooi). Dit veroorsaak dan irritasie in die longe wat kan lei tot koors, slaperigheid, vinnige asemhaling en 'n bors wat toetrek.
Ons weet dat paraffien irritasie in die longe veroorsaak, maar ons is nie seker of dit lei tot infeksie nie. As dit wel infeksie veroorsaak sou ons dit met 'n antibiotika behandel, maar vorige studies het bewys dat daar geen verskil is in die verbetering van kinders wat antibiotika ontvang teenoor die wat nie antibiotika ontvang het nie. Die huidige praktyk by Rooi Kruis hospitaal is om nie antibiotika te gee na 'n kind paraffien gedrink het nie. In hierdie studie hoop ons om uit te vind of kinders wat wel antibiotika neem vinniger beter word.

Hoe sal die studie gedoen word?
'n Dokter sal u kind volledig ondersoek.
U kind se temperatuur, polsspoed, asemhalingspoed en bloedsuurstofvlakke sal gedurende sy/haar opname gereeld getoets word.

Hy/sy sal met 'n medisynebottel ontvang wat of 'n ware antibiotika sal bevat, of 'n mengsel wat dieselfde lyk en proe, maar wat geen antibiotika bevat nie (dit word 'n placebo genoem). Nie u of u dokter sal weet watter tipe bottel u kind ontvang het nie.
Afhangende van die hoeveelheid paraffien wat in u kind se longe beland het, sal ons verwag dat hy/sy binne 6 tot 72 uur verbeter. As hy/sy nie beter word nie sal hy/sy ondersoek word deur een van die dokters wat weet wat in elke bottle is, en dan daarvolgens behandel word.
Dit is baie belangrik dat u nie die medisyne vir enige iemand anders by die huis gebruik nie.

Enige ander behandeling soos suurstof, Panado, of 'n nebuliseerder sal gegee word soos nodig. U kind mag dalk 'n bloedtoets benodig wat ons met 'n vingerprik kan doen. Gedurende sy/haar hospitaal verblyf sal ons ook 'n X-straal van die longe neem. Dit is standaard prosedure by kinders wat paraffien gedrink het.

U kind sal moet terugkom vir twee besoeke in die eerste week na onstlag. Hy/sy sal ondersoek word en u kan ons dan ook inlig aangaande sy/haar vordering en simptome.
Die onkoste vir u vervoer sal deur die navorsingsprojek gedek word en u afspraak sal op 'n spesifieke tyd wees wat vir u, u kind en die dokter sal pas. U sal nie in 'n ry hoef te wag saam met die algemene pasiente nie, maar sal onmiddelik gehelp word.

Wat beteken hierdie studie vir u en u kind?
U kind sal dieselfde behandeling ontvang as alle kinders wat paraffien ingeneem het.
Hierdie behandeling veroorsaak geen ernstige newe-effekte nie. Die antibiotika word algemeen gebruik vir u kind se toestand, en vir baie ander kinders met ander tipe long infeksies. Aangesien studies sover bevind het dat daar geen verskil is tussen kinders wat antibiotika kry teenoor die wat dit nie kry nie, is daar geen gevaar as u kind 'n placebo neem nie.

Die voordeel is dat u kind voldoende behandeling en opvolging sal kry gedurende sy/haar siekte. Die studie sal voordelig wees vir toekomstige kinders wat asemhalingsprobleme ontwikkel na die inname van paraffien, want dit sal ons help om te weet of antibiotika bydra daartoe om hulle beter te maak.

Vertroulikheid
U kind se mediese rekords met betrekking tot hierdie studies sal vertroulik gehou word. Nie u of u kind se naam sal genoem word in enige publikasie wat uit hierdie studie mag volg nie.

Vrywillige deelname
Dit is u vrywillige keuse om u kind aan hierdie studie te laat deelneem. Die behandeling wat u kind sal ontvang sal geensins geaffekteer word indien hy/sy nie aan die studie sou deelneem nie.

Hiermee verklaar ek dat ek die vorm gelees het en verstaan. My vrae is volledig beantwoord. Ek gee hiermee vrywilliglik toestemming dat my kind aan hierdie studie mag deelneem.

Ek,_____, die ouer/ wettige voog van

_____ gee hiermee toestemming dat hy/sy

mag deelneem aan hierdie studie.

Geteken: _____ Getuie: _____

Datum: _____ Datum: _____

Appendix B3
(XHOSA)
ULWAZI KUMGULI NEFOMU YEMVUME

"Ukusetyenziswa kwee-antibhayothikhi ezinqanda usulelo kulawulo lwesigulo semiphunga emva kokusela iparafini"

Wena nomntwana wakho niyacelwa ukuba nithathe inxaxheba kufundo olungophando kwezamayeza kwiSibhedlele Sabantwana Somnqamlezo Obomvu. Olu lwazi lulandelayo luchaza olu fundo nendima yomntwana wakho njengomthathi-nxaxheba. Nceda ufunde ngenyameko ubuze xa ungaqondi.

Intsusa nesizathu solu fundo
Umntwana wakho ulele esibhedlele ngenxa yokusela iparafini. Iparafini inokuphefumlelwa ngaphakathi xa iselwayo okanye inokunyuka ivela esiswini, ngakumbi ukuba uyakhupha, iye kungena emiphungeni. Le nto yenza uthukuthezelo emiphungeni kwaye ingabanga ifiva, ukozela, ukuphefumla ngokukhawuleza, mhlawumbi nokuxinana kwesifuba. Siyazi ukuba iparafini inokubanga uthukuthezelo emiphungeni kodwa asiqinisekanga ukuba ibanga usulelo. Ukuba iyalwenza usulelo singasebenzisa iantibhayothikhi kodwa ezinye izifundo zibonise ukuba akukho mahluko ekubeni ngcono phakathi kwabasebenzise i-antibhayothikhi nabangayisebenzisanga. KwiSibhedlele Somnqamlezo Obomvu asibaniki antibhayothikhi abantwana abasele iparafini. Kolu fundo sinethemba lokufumanisa ukuba ngaba abantwana abanikwe i-antibhayothikhi baba ngcono msinyane na kunabangayinikwanga.

Luza kwenziwa njani olu fundo?
Ugqirha uya kumxilongisisa umntwana wakho. Umntwana wakho uya kuthathwa ubushushu, ukubetha kwentliziyo, ukuphefumla nobungakanani be-oksijini egazini rhoqo ngexesha engaphakathi kwesibhedlele.

Uya kunikwa i-imbodlela yeyeza. Imbodlela yeyeza iya kuba ne-antibhayothikhi yokwenene okanye umxube okhangeleka nonencasa efana ncam nayo nangona ungena-antibhayothikhi (Le nto kuthiwa yiplasibho). Wena kwanogqira aniyi kwazi ukuba umntwana wakho unikwe ntoni.
Ngokuxhomekeke ekubeni ingakanani iparafini engene emiphungeni yomntwana wakho, simlindele ukuba abengcono ukususela kwiiyure ezi-6-72. Ukuba akabingcono, uya kubonana nomye woogqirha owaziyo ukuba kukho ntoni kwimbodlela nganye aze anyangwe ngokufanelekileyo.
Kubalulekile ukuba olu nyango lungasetyenziswa nakubani na ongomnye ekhaya.

Naluphi na unyango olungaphaya, njenge-oksijini, iphanado nokuvulwa kweentunja zomoya zemiphunga luya kunikwa xa lufuneka. Umntwana wakho kungafuneka enziwe uvavanyo-gazi, olunokwenziwa ngokuxholwa emnweni. Oku kuvavanya ukuba kukho usulelo na. Umntwana wakho uya kwenziwa iX-reyi yesifuba. Oku kwenziwa ngokwesiqhelo ukuphonononga abantwana abangeniswe emva kokusela iparafini.

Emva kokuba umntwana wakho ekhutshiwe esibhedlele, kuya kufuneka abuye izihlandlo ezibini kwiveki yokuqala. Uya kuphinda axilongwe uze usixelele ngenkqubo yakhe

neempawu azibonisayo. Iindleko zokukhwela ziya kuhlawulwa lufundo lophando, ixesha lokubonana nogqirha liya kulungiselela wena, umntwana nogqirha. Aniyi kuma emgceni. Niya kubonwa kwangoko.

Olu fundo luthetha ntoni kuwe nomntwana wakho?
Umntwana wakho uyakunyangwa njengaye nawuphi na umntwana osele iparafini. Akukho ziqhamo zibi zingamandla kolu nyango. I-antibhayothikhi isetyenziselwa imeko yomntwana wakho ngokuqhelekileyo. Iyasetyenziswa nakubantwana abanosulelo lwesifuba olwahlukileyo. Ezi zizifundo ezibonisa ukungabikho komahluko phakathi kokunika i-antibhayothikhi emva kokuselwa kweparafini nokungayiniki, ngoko ke akukho ngozi xa umntwana wakho efumana iplasibho.

Inzuzo kumntwana wakho iya kuba kukufumana unyango olupheleleyo nonyamekelo ngexesha lokugula kwakhe. Olu fundo luyakunceda abantwana bengomiso abaphefumla nzima emva kokusela iparafini kuba iyakusinceda sazi ukuba ii-antibhayothikhi ziyawenza umahluko ekubeni ngcono kusini na.

Okulihlebo
Iirekhodi zofundo zomntwana wakho ziya kugcinwa zilihlebo. Igama lakho nelomntwana wakho aliyi kuvela nakuluphi na upapasho lolu fundo olungabakho.

Ukuthatha inxaxheba ngokuzithandela
Ukuthatha inxaxheba komntwana wakho kolu fundo kuxhomekeke kuwe. Ungakhetha ukungathathi nxaxheba kolu fundo. Loo nto ayiyi kuchaphazela unyango oluya kufunyanwa ngumntwana wakho.

Ndiyifundile ndayiqonda le fomu. Imibuzo yam iphendulekile. Ndiyavuma, ngokuzithandela, ukuba umntwana wam athathe inxaxheba kolu fundo.

Mna,_____,umzali/umgcini

ka_____ ndiyavuma ukuba athathe

inxaxheba kolu fundo.

Kusayine:_____ Ingqina:_____

Umhla:_____ Umhla_____

Istikha somguli:

Appendix C

PARAFFIN INGESTION STUDY – ADMISSION QUESTIONNAIRE

Admitting doctor:_____ Patient details (attach sticker)
Date and time:_____
Study drug bottle batch number:_____

PARAFFIN HISTORY

Date and time of ingestion:_____ Witnessed? Yes/No
Paraffin? Suspected/Known Amount ingested (estimated):_____
Coughed during ingestion? Yes/No/ Subsequently? Yes/No
Given milk/other emetic? Yes/No Details of other emetic:_____
Vomited? Yes/No Number of times?_____
Referred? Yes/No Details:_____
Medication prior to referral? Yes/No Details:_____
Other comments:_____

MEDICAL HISTORY

Pre-existing respiratory illness? Yes/No Details:_____
Current/recent medications:_____
Previous medical history:_____
TB? Currently/past/never Details:_____
TB contact? Yes/No Details:_____
HIV status? exposed/positive/negative/unknown Details:_____
Antenatal history:_____
Immunisations?_____

EXAMINATION

Weight:_____ Temperature:_____
Pulse rate:_____ Respiratory rate:_____
Pulse oximetry:_____ Oxygen? Yes/No Amount:_____

General: Cyanosis? Yes/No
Other:_____

Chest: Recessions? Yes/No Mild/moderate/severe
Flaring? Yes/No Grunting? Yes/No
Wheeze? Yes/No Crepitations? Yes/No
If any localisation, specify: _____
CNS: Drowsy? Yes/No
Other:_____
CVS:_____
Abdomen:_____
ENT:_____
Other comments:_____

INVESTIGATIONS

CXR (please draw picture)

Appendix D1 **Patient number_____**

CASE REPORT FORMS **Bottle batch number_____**

Admitting doctor:_____

Admission date and time:_____ Hours post ingestion:_____

Discharge date and time:_____ Hours spent in hospital:_____

Patient details (attach sticker)

Parent contact details:

_____

_____

PARAFFIN HISTORY

Date and time of ingestion:_____ Witnessed? Yes/No

Paraffin? Suspected/Known Amount ingested (estimated):_____

Where was paraffin stored? _____ What container?_____

Coughed during ingestion Yes/No Subsequently? Yes/No

Given milk/other emetic? Yes/No Details of other emetic:_____

Vomited? Yes/No If yes, how many times?_____

Referred? Yes/No Details:_____

Medication prior to referral? Yes/No Details:_____

Other comments:_____

MEDICAL HISTORY

Pre-existing respiratory illness? Yes/No Details:_____

Current/recent medications:_____

Previous medical history:_____

TB? Currently/past/never Details:_____

TB contact? Yes/No Details:_____

HIV status? exposed/positive/negative/unknown Details:_____

Immunisations?_____

ANTENATAL HISTORY

Gestational age:_____ Birthweight:_____

Other details:_____

SOCIAL HISTORY

Residential area:_____

Household amenities: Water _____

Sanitation _____

Electricity _____

Level of education: Mother_____

Father_____

Other caregiver_____

Smokers in household? Yes/No Who?_____

ADMISSION EXAMINATION

Weight (kg):_____ Height (cm):_____

Centile: _____

Temperature:_____ Pulse rate:_____

Respiratory rate:_____ Pulse oximetry:_____

Oxygen? Yes/No Amount:_____

General: Cyanosis? Yes/No

Other:_____

Chest: Recessions? Yes/No Mild/moderate/severe

Flaring? Yes/No Grunting? Yes/No

Wheeze? Yes/No Crepitations? Yes/No

If any localisation, specify:_____

CNS: Drowsy? Yes/No

Other:_____

CVS:_____

Abdomen:_____

ENT:_____

Other comments:_____

_____

INVESTIGATIONS

CXR (please draw picture)

FURTHER ASSESSMENTS

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CLINICAL FINDINGS DURING ENROLMENT IN STUDY

Date and time: _____
Hours post ingestion:_____

Temperature:_____ Pulse rate:_____
Respiratory rate:_____ Pulse oximetry:_____ _____
Oxygen? Yes/No Amount:_____

General: Cyanosis? Yes/No
Other:_____

Chest: Recessions? Yes/No Mild/moderate/severe
Flaring? Yes/No Grunting? Yes/No
Wheeze? Yes/No Crepitations? Yes/No
If any localisation, specify:_____
CNS: Drowsy? Yes/No
Other:_____
CVS:_____
Abdomen:_____
ENT:_____

FURTHER COMMENTS:
(See separate sheets for complete record of observations)

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Appendix D2
FOLLOW-UP 1

Date and time:_____
Inpatient/outpatient?_____
Bottle batch number:_____
Volume of antibiotic remaining:_____

SYMPTOMS:
Cough? Yes/No Improving/static/deteriorating
Wheeze? Yes/No Improving/static/deteriorating
Shortness of breath? Yes/No Improving/static/deteriorating
Fever? Yes/No Improving/static/deteriorating
Other:
Attended clinic/another doctor since discharge?_____
Details:_____

EXAMINATION
Temperature:_____ Pulse rate:_____
Respiratory rate:_____ Pulse oximetry:_____
Oxygen? Yes/No Amount:_____

General: Cyanosis? Yes/No
Other:_____
Chest: Recessions? Yes/No Mild/moderate/severe
Flaring? Yes/No Grunting? Yes/No
Wheeze? Yes/No Crepitations? Yes/No
If any localisation, specify: _____
CNS: Drowsy? Yes/No
Other:_____
CVS:_____
Abdomen:_____
ENT:_____

FURTHER INVESTIGATIONS:
_____
_____
_____
_____

OTHER COMMENTS:
_____
_____
_____
_____
_____
_____

Appendix D3
FOLLOW-UP 2

Date and time:_____
Inpatient/outpatient?_____
Bottle batch number:_____
Volume of antibiotic remaining:_____

SYMPTOMS:
Cough? Yes/No Improving/static/deteriorating
Wheeze? Yes/No Improving/static/deteriorating
Shortness of breath? Yes/No Improving/static/deteriorating
Fever? Yes/No Improving/static/deteriorating
Other:

Attended clinic/another doctor since discharge?_____
Details:_____

EXAMINATION
Temperature:_____ Pulse rate:_____
Respiratory rate:_____ Pulse oximetry:_____
Oxygen? Yes/No Amount:_____

General: Cyanosis? Yes/No
Other:_____
Chest: Recessions? Yes/No Mild/moderate/severe
Flaring? Yes/No Grunting? Yes/No
Wheeze? Yes/No Crepitations? Yes/No
If any localisation, specify: _____
CNS: Drowsy? Yes/No
Other:_____
CVS:_____
Abdomen:_____
ENT:_____

FURTHER INVESTIGATIONS:
_____
_____
_____
_____

OTHER COMMENTS:
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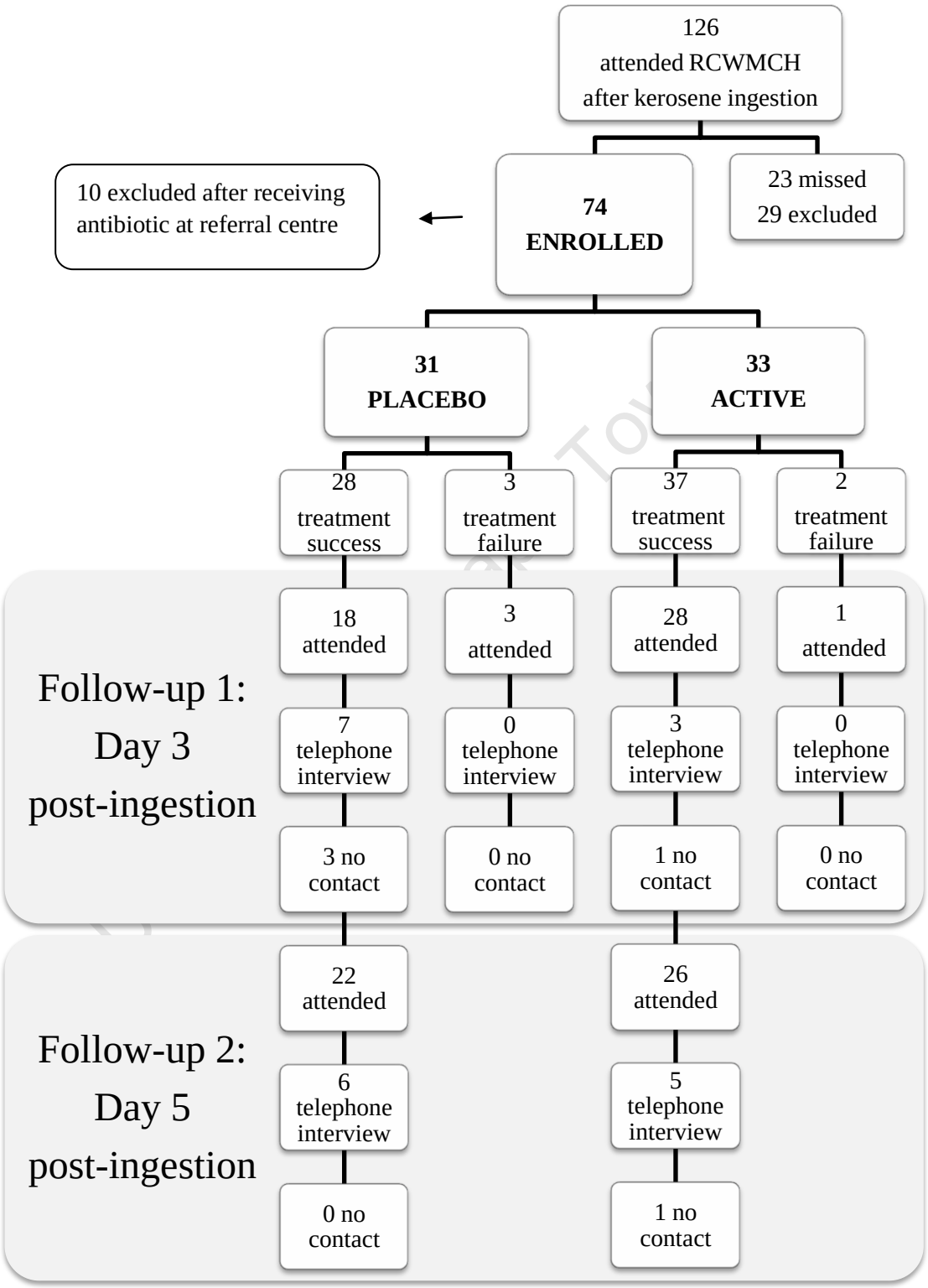
Appendix E1: The flow of study participants through enrolment and follow-up, excluding those who received an antibiotic at the referral centre before enrolment



Appendix E2: Baseline characteristics, event details and possible confounding conditions and risk factors for placebo and active groups, excluding those who received an antibiotic at the referral centre before enrolment

	PLACEBO ***n*** **= 31**	**ACTIVE** ***n*** **= 33**	***P*** **value**
PATIENT MEASUREMENTS			
Male:female, *n* (%)	18:13 (58:42)	20:13 (61:39)	>0.05
Age (months)*	18 (15-21)	20 (16-27)	>0.05
Weight (kg)*	11.8 (10.1-12.8)	11.4 (10.1-12.9)	>0.05
INGESTION EVENT, *n* (%)			
Hours post-ingestion at enrolment*	6.0 (3.5-10.0)	6.0 (3.5-8.0)	>0.05
Season			>0.05
Spring	8 (26)	9 (27)	
Summer	9 (29)	9 (27)	
Autumn	4 (13)	4 (12)	
Winter	10 (32)	11 (33)	
Witnessed	10 (32)	9 (27)	>0.05
Occurred at home	17 (55)	22 (67)	>0.05
Container			>0.05
Paraffin bottle	8 (26)	8 (24)	
Juice bottle	18 (58)	20 (61)	
Other (paraffin lamp)	1 (3)	1 (3)	
Given milk and/or water at place of ingestion	21 (68)	25 (76)	>0.05
POSSIBLE CONFOUNDING CONDITIONS**,** *n* (%)			
Upper respiratory tract infection (URTI)			>0.05
Preceding	8 (26)	6 (18)	
New-onset	13 (42)	13 (39)	
Active TB disease	2 (6)	1 (3)	>0.05
POSSIBLE RISK FACTORS**,** *n* (%)			
Vomiting post-ingestion	18 (58)	19 (58)	>0.05
Age categories (months)			>0.05
12-23	25 (81)	24 (73)	
24-35	5 (16)	7 (21)	
> 36	1 (3)	2 (6)	
Smoking contact	11 (35)	9 (27)	>0.05
HIV exposed	11 (35)	7 (21)	>0.05
Prior respiratory history	5 (16)	10 (30)	>0.05
Formal housing	13 (42)	7 (21)	>0.05
Electricity	26 (84)	20 (61)	>0.05
Educational status (mother)			>0.05
< 10 years formal education	7 (23)	9 (27)	
> 10 years formal education	17 (55)	20 (61)	
Tertiary	7 (23)	4 (12)	

*Values are median (interquartile range)

Appendix E3: Clinical presentation for placebo and active groups, excluding those who received an antibiotic at the referral centre before enrolment

	PLACEBO ***n*** **= 31**	**ACTIVE** ***n*** **= 33**	***P*** **value**
INCLUSION CRITERIA, *n* (%)			
Symptoms only	6 (19)	6 (18)	>0.05
Signs only	1 (3)	1 (3)	>0.05
Symptoms and signs	24 (77)	26 (79)	>0.05
SYMPTOMS, *n* (%)			
History of coughing	30 (97)	32 (97)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	48 (37-60)	44 (30-58)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	7 (23)	7 (21)	
Severe (> 50bpm)	10 (32)	10 (30)	
Recessions			>0.05
Mild	7 (23)	7 (21)	
Moderate	1 (3)	2 (6)	
Flaring	9 (29)	10 (30)	>0.05
Grunting	6 (19)	5 (15)	>0.05
Wheeze	2 (6)	4 (12)	>0.05
Crepitations			>0.05
Localised	4 (13)	4 (12)	
Diffuse	4 (13)	4 (12)	
Temperature (˚C)*	37.3 (36.7-38.3)	37.2 (36.7-38.4)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	7 (23)	6 (18)	
Severe (> 38.5˚C)	6 (19)	8 (24)	
Altered mental status	8 (26)	8 (24)	>0.05

*Values are median (interquartile range)
bpm = breaths per minute

Appendix E4: Summary of outcomes measures for placebo and active groups, excluding those who received an antibiotic at the referral centre before enrolment

	PLACEBO	**ACTIVE**	***P* value**
PRIMARY, *n* (%)	***n* = 31**	***n* = 33**	
Treatment success	28 (90)	32 (97)	>0.05
Treatment failure	3 (10)	1 (3)	>0.05
SECONDARY			
Stay in hospital (days)*	0.5 (0-1.0)	0.5 (0-1.0)	>0.05
Day 3 post-ingestion, *n* (%)	***n* = 21**	***n* = 29**	
Absent symptoms and signs	5 (24)	6 (21)	>0.05
Symptoms only	2 (10)	7 (24)	>0.05
Signs only	1 (5)	2 (7)	>0.05
Symptoms and signs	13 (62)	14 (48)	>0.05

*Values are median (interquartile range)

Appendix E5: Follow-up for placebo and active groups, excluding those who received an antibiotic at the referral centre before enrolment

	DAY 3 POST-INGESTION		
	PLACEBO	**ACTIVE**	***P* value**
SYMPTOMS**,** *n* (%)	*n* = 28†	*n* = 32	
Cough			>0.05
Asymptomatic	15 (54)	17 (53)	
Symptomatic	12 (43)	15 (47)	
Wheeze			>0.05
Asymptomatic	23 (82)	27 (84)	
Symptomatic	4 (14)	5 (16)	
Shortness of breath			>0.05
Asymptomatic	21 (75)	26 (81)	
Symptomatic	6 (21)	6 (19)	
Fever			>0.05
Asymptomatic	16 (57)	21 (66)	
Symptomatic	11 (39)	11 (34)	
SIGNS, *n* (%)	*n* = 21	*n* = 29	
Respiratory rate (bpm)*	36 (33-47)	36 (32-42)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	4 (19)	6 (21)	
Severe (> 50bpm)	4 (19)	3 (10)	
Recessions (mild)	1 (5)	0 (0)	>0.05
Flaring	3 (14)	4 (14)	>0.05
Grunting	2 (10)	0 (0)	>0.05
Wheeze	3 (14)	2 (7)	>0.05
Crepitations			>0.05
Localised	3 (14)	6 (21)	
Diffuse	1 (5)	3 (10)	
Temperature (˚C)*	36.8 (36.5-37.4)	36.6 (36.1-37.1)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	4 (19)	1 (3)	
Severe (> 38.5˚C)	1 (5)	2 (7)	
Altered mental status	4 (19)	7 (24)	>0.05

*Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

bpm = breaths per minute

Appendix E6: Description of changes in reported symptoms from previous assessment for placebo and active groups, excluding those who received an antibiotic at the referral centre before enrolment

	DAY 3 POST-INGESTION		
	PLACEBO	**ACTIVE**	***P* value**
SYMPTOMS**,** *n* (%)	*n* = 28*	*n* = 32	
Cough			>0.05
Absent or resolved	15 (54)	17 (53)	
Improving	6 (21)	12 (38)	
Static	3 (11)	2 (6)	
Deteriorating	3 (11)	1 (3)	
Wheeze			>0.05
Absent or resolved	23 (82)	27 (84)	
Improving	3 (11)	3 (9)	
Static	1 (4)	2 (6)	
Deteriorating	0 (0)	0 (0)	
Shortness of breath			>0.05
Absent or resolved	21 (75)	26 (81)	
Improving	3 (11)	3 (9)	
Static	1 (4)	3 (9)	
Deteriorating	2 (7)	0 (0)	
Fever			>0.05
Absent or resolved	16 (57)	21 (66)	
Improving	7 (25)	6 (19)	
Static	4 (14)	4 (13)	
Deteriorating	0 (0)	1 (3)	

*Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

Appendix F1: Clinical presentation according to vomiting post-ingestion

	No vomiting *n* = 32†	**Vomited *n* = 41†**	***P* value**
SYMPTOMS, *n* (%)			
History of coughing	32 (100)	39 (95)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	48 (39-60)	43 (35-55)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	11 (34)	9 (22)	
Severe (> 50bpm)	11 (34)	11 (27)	
Recessions			>0.05
Mild	7 (22)	9 (22)	
Moderate	2 (6)	2 (5)	
Flaring	13 (41)	10 (24)	>0.05
Grunting	5 (16)	7 (17)	>0.05
Wheeze	4 (13)	3 (7)	>0.05
Crepitations			>0.05
Localised	5 (16)	4 (10)	
Diffuse	5 (16)	7 (17)	
Temperature (˚C)*	37.3 (36.5-38.2)	37.2 (36.7-38.4)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	9 (28)	6 (15)	
Severe (> 38.5˚C)	5 (16)	10 (24)	
Altered mental status	9 (28)	10 (24)	>0.05

*Values are median (interquartile range)

†Total does not add up to 74 as in one study participant it was unknown if he vomited post-ingestion

bpm = breaths per minute

Appendix F2: Follow-up according to vomiting post-ingestion

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	No vomiting	**Vomited**	***P***	**No vomiting**	**Vomited**	***P***
SYMPTOMS, *n* (%)†	*n* = 31	*n* = 37		*n* = 27	*n* = 39	
Cough			>0.05			>0.05
Absent or resolved	18 (58)	20 (54)		15 (56)	24 (62)	
Improving	11 (35)	10 (27)		7 (26)	11 (28)	
Static	1 (3)	4 (11)		1 (4)	2 (5)	
Deteriorating	1 (3)	3 (8)		4 (15)	2 (5)	
Wheeze			>0.05			>0.05
Absent or resolved	25 (81)	33 (89)		25 (93)	35 (90)	
Improving	5 (16)	2 (5)		0 (0)	3 (8)	
Static	1 (3)	2 (5)		0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)		2 (7)	1 (3)	
Shortness of breath			>0.05			>0.05
Absent or resolved	27 (87)	27 (73)		26 (96)	35 (90)	
Improving	1 (3)	7 (19)		1 (4)	2 (5)	
Static	1 (3)	3 (8)		0 (0)	0 (0)	
Deteriorating	2 (6)	0 (0)		0 (0)	2 (5)	
Fever			>0.05			>0.05
Absent or resolved	17 (55)	25 (68)		21 (78)	31 (79)	
Improving	9 (29)	8 (22)		4 (15)	4 (10)	
Static	5 (16)	3 (8)		1 (4)	1 (3)	
Deteriorating	0 (0)	1 (3)		1 (4)	3 (8)	
SIGNS, *n* (%)†	*n* = 26	*n* = 33		*n* = 23	*n* = 31	
Respiratory rate (bpm)*	38 (34-45)	36 (31-44)	>0.05	36 (32-44)	36 (31-40)	>0.05
Respiratory rate severity			>0.05			>0.05
Mild to moderate (41-50bpm)	3 (12)	10 (30)		6 (26)	7 (23)	
Severe (> 50bpm)	6 (23)	3 (9)		0 (0)	0 (0)	
Recessions (mild)	1 (4)	1 (3)	>0.05	1 (4)	0 (0)	>0.05
Flaring	6 (23)	2 (6)	>0.05	1 (4)	0 (0)	>0.05
Grunting	2 (8)	1 (3)	>0.05	0 (0)	0 (0)	>0.05
Wheeze	2 (8)	3 (9)	>0.05	1 (4)	0 (0)	>0.05
Crepitations			>0.05			>0.05
Localised	4 (15)	5 (15)		2 (9)	1 (3)	
Diffuse	3 (12)	3 (9)		1 (4)	0 (0)	
Temperature (˚C)*	36.9 (36.4-37.3)	36.7 (36.3-37.1)	>0.05	36.5 (36.3-36.9)	36.5 (36.2-36.9)	>0.05
Temperature severity			>0.05			>0.05
Mild to moderate (37.5–38.5˚C)	3 (12)	4 (12)		0 (0)	0 (0)	
Severe (> 38.5˚C)	1 (4)	3 (9)		0 (0)	0 (0)	
Altered mental status	6 (23)	6 (18)	>0.05	2 (9)	0 (0)	>0.05

*Values are median (interquartile range)

†Totals (symptoms and signs) are missing one study participant in whom it was unknown if he vomited post-ingestion

bpm = breaths per minute

Appendix G1: Clinical presentation according to a household smoking contact

	No smoking contact *n* = 46†	**Smoking contact *n* = 26†**	***P* value**
SYMPTOMS, *n* (%)			
History of coughing	46 (100)	23 (88)	>0.05
History of vomiting	26 (57)	14 (54)	>0.05
SIGNS, *n* (%)			
Respiratory rate (bpm)*	44 (35-56)	48 (39-61)	>0.05
Respiratory rate severity			>0.05
Mild to moderate (41-50bpm)	12 (26)	9 (35)	
Severe (> 50bpm)	11 (24)	9 (35)	
Recessions			>0.05
Mild	8 (17)	7 (27)	
Moderate	4 (9)	0 (0)	
Flaring	14 (30)	10 (38)	>0.05
Grunting	19 (41)	3 (12)	>0.05
Wheeze	6 (13)	1 (4)	>0.05
Crepitations			>0.05
Localised	5 (11)	4 (15)	
Diffuse	5 (11)	7 (27)	
Temperature (˚C)*	37.3 (36.9-38.2)	37.0 (36.6-38.4)	>0.05
Temperature severity			>0.05
Mild to moderate (37.5–38.5˚C)	10 (22)	5 (19)	
Severe (> 38.5˚C)	9 (20)	6 (23)	
Altered mental status	10 (22)	9 (35)	>0.05

*Values are median (interquartile range)

†Total does not add up to 74 as in two study participants it was unknown if they had a household smoking contact

bpm = breaths per minute

Appendix G2: Follow-up according to a household smoking contact

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	No smoking contact	**Smoking contact**	***P***	**No smoking contact**	**Smoking contact**	***P***
SYMPTOMS**,** *n* (%)†	*n* = 45‡	*n* = 23		*n* = 41‡	*n* = 25	
Cough			>0.05			>0.05
Absent or resolved	24 (53)	13 (57)		25 (61)	13 (52)	
Improving	15 (33)	6 (26)		11 (27)	7 (28)	
Static	2 (4)	3 (13)		2 (5)	1 (4)	
Deteriorating	3 (7)	1 (4)		2 (5)	4 (16)	
Wheeze			>0.05			>0.05
Absent or resolved	38 (84)	19 (83)		37 (90)	22 (88)	
Improving	5 (11)	2 (9)		2 (5)	1 (4)	
Static	1 (2)	2 (9)		0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)		1 (2)	2 (8)	
Shortness of breath			>0.05			>0.05
Absent or resolved	36 (80)	17 (74)		39 (95)	21 (84)	
Improving	3 (7)	5 (22)		0 (0)	3 (12)	
Static	3 (7)	1 (4)		0 (0)	0 (0)	
Deteriorating	2 (4)	0 (0)		1 (2)	1 (4)	
Fever			>0.05			>0.05
Absent or resolved	25 (56)	16 (70)		33 (80)	17 (68)	
Improving	13 (29)	4 (17)		3 (7)	6 (24)	
Static	6 (13)	2 (9)		1 (2)	1 (4)	
Deteriorating	0 (0)	1 (4)		3 (7)	1 (4)	
SIGNS, *n* (%)	*n* = 38	*n* = 21		*n* = 35†	*n* = 19†	
Respiratory rate (bpm)*	38 (32-43)	36 (33-46)	>0.05	35 (28-40)	38 (35-44)	<0.05
Respiratory rate severity			>0.05			>0.05
Mild to moderate (41-50bpm)	8 (21)	5 (24)		6 (17)	6 (32)	
Severe (> 50bpm)	6 (16)	3 (14)		0 (0)	0 (0)	
Recessions (mild)	2 (5)	0 (0)	>0.05	0 (0)	1 (5)	>0.05
Flaring	7 (18)	1 (5)	>0.05	1 (3)	0 (0)	>0.05
Grunting	3 (8)	0 (0)	>0.05	0 (0)	0 (0)	>0.05
Wheeze	5 (13)	0 (0)	>0.05	0 (0)	1 (5)	>0.05
Crepitations			>0.05			>0.05
Localised	5 (13)	4 (19)		1 (3)	2 (11)	
Diffuse	5 (13)	1 (5)		1 (3)	0 (0)	
Temperature (˚C)*	36.9 (36.3-37.3)	36.7 (36.4-37.3)	>0.05	36.5 (36.2-36.8)	36.7 (36.5-37.0)	<0.05
Temperature severity			>0.05			>0.05
Mild to moderate (37.5–38.5˚C)	5 (13)	2 (10)		0 (0)	0 (0)	
Severe (> 38.5˚C)	1 (3)	3 (14)		0 (0)	0 (0)	
Altered mental status	7 (18)	5 (24)	>0.05	1 (3)	1 (5)	>0.05

*****Values are median (interquartile range)

†Totals (symptoms and signs) are missing two patients in whom it was unknown if they had a household smoking contact

‡Where values do not add up to the denominator (*n* = symptoms), data were not recorded for the missing number

bpm = breaths per minute

Appendix H: Follow-up according to a prior respiratory history

	DAY 3 POST-INGESTION			DAY 5 POST-INGESTION		
	No resp history	**Resp history**	***P***	**No resp history**	**Resp history**	***P***
SYMPTOMS**,** *n* (%)	*n* = 52†	*n* = 17		*n* = 52	*n* = 16†	
Cough			>0.05			>0.05
Absent or resolved	27 (52)	11 (65)		31 (60)	9 (56)	
Improving	15 (29)	6 (35)		16 (31)	2 (13)	
Static	5 (10)	0 (0)		1 (2)	2 (13)	
Deteriorating	4 (8)	0 (0)		4 (8)	2 (13)	
Wheeze			>0.05			>0.05
Absent or resolved	43 (83)	15 (88)		48 (92)	13 (81)	
Improving	5 (10)	2 (12)		3 (6)	0 (0)	
Static	3 (6)	0 (0)		0 (0)	0 (0)	
Deteriorating	0 (0)	0 (0)		1 (2)	2 (13)	
Shortness of breath			>0.05			>0.05
Absent or resolved	40 (77)	14 (82)		49 (94)	13 (81)	
Improving	6 (12)	2 (12)		2 (4)	1 (6)	
Static	4 (8)	0 (0)		0 (0)	0 (0)	
Deteriorating	1 (2)	1 (6)		1 (2)	1 (6)	
Fever			>0.05			>0.05
Absent or resolved	28 (54)	14 (82)		38 (73)	14 (88)	
Improving	14 (27)	3 (18)		9 (17)	0 (0)	
Static	8 (15)	0 (0)		1 (2)	1 (6)	
Deteriorating	1 (2)	0 (0)		4 (8)	0 (0)	
						>0.05
SIGNS, *n* (%)	*n* = 45	*n* = 14		*n* = 40	*n* = 15	
Respiratory rate (bpm)*	37 (32-47)	39 (28-42)	>0.05	36 (31-42)	36 (32-40)	>0.05
Respiratory rate severity			>0.05			>0.05
Mild to moderate (41-50bpm)	8 (18)	5 (36)		10 (25)	3 (20)	
Severe (> 50bpm)	8 (18)	1 (7)		0 (0)	0 (0)	
Recessions (mild)	1 (2)	1 (7)	>0.05	1 (3)	0 (0)	>0.05
Flaring	6 (13)	2 (14)	>0.05	0 (0)	1 (7)	>0.05
Grunting	2 (4)	1 (7)	>0.05	0 (0)	0 (0)	>0.05
Wheeze	5 (11)	0 (0)	>0.05	0 (0)	1 (7)	>0.05
Crepitations			>0.05			>0.05
Localised	6 (13)	3 (21)		2 (5)	1 (7)	
Diffuse	6 (13)	0 (0)		1 (3)	0 (0)	
Temperature (˚C)*	36.8 (36.4-37.3)	36.7 (36.2-37.3)	>0.05	36.6 (36.3-36.9)	36.5 (36.2-36.7)	>0.05
Temperature severity			>0.05			>0.05
Mild to moderate (37.5–38.5˚C)	3 (7)	4 (29)		0 (0)	0 (0)	
Severe (> 38.5˚C)	2 (4)	2 (14)		0 (0)	0 (0)	
Altered mental status	10 (22)	2 (14)	>0.05	2 (5)	0 (0)	>0.05

*****Values are median (interquartile range)

†Where values do not add up to the denominator (*n* = symptoms), data were not recorded or unknown for the missing number

Resp = respiratory

bpm = breaths per minute

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