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A multicentre pragmatic randomised controlled equivalence trial comparing oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children
PIVOT Trial

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Abstract

Objective

To ascertain whether therapeutic equivalence exists for treatment of paediatric community acquired pneumonia by the oral and intravenous (IV) routes.

Design

Multicentre pragmatic randomised controlled non-blinded equivalence trial. Equivalence was defined as no more than a 20% difference between treatments of the proportion meeting the primary outcome measure at any time.

Setting

Eight paediatric centres in England (district general and tertiary hospitals).

Participants

246 children who required admission to hospital and met the following 3 criteria for diagnosis of pneumonia: fever, respiratory symptoms or signs and radiologically confirmed pneumonia. Exclusion criteria were wheeze, oxygen saturations < 85% in air, shock requiring > 20mls/kg fluid resuscitation, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy and age < 6 months.

Intervention

Children were randomised to oral amoxicillin (126) or IV benzyl penicillin (120). The oral group received 7 days oral treatment. The IV group were changed to oral amoxicillin after a median of 6 doses IV and received 7 days of antibiotics in total.

Main Outcome Measures

The pre-defined primary outcome measure was time for the temperature to be less than 38^{o}C for 24 continuous hours and oxygen requirement to cease. Secondary outcomes were time in hospital, complications, duration of oxygen requirement and time to resolution of illness.

Results

Oral amoxicillin and IV benzyl penicillin were shown to be equivalent. Median time for temperature to settle was 1.3 days in both groups (p=0.0001 for equivalence). Three children in the oral group were changed to IV antibiotics. Seven children in the IV group were changed to different IV antibiotics. Median time to complete resolution of symptoms was 9 days in both groups.

Conclusion

The findings demonstrate that oral amoxicillin is effective for the majority of children admitted to hospital with pneumonia (all but those with the most severe disease who were excluded from this study). Prior to this study, the British Thoracic Society (BTS) guidelines on childhood pneumonia could not draw on evidence to address this issue. Most importantly, this will spare children and their families the trauma and pain of cannulation and children spend less time in hospital.

Trial Registration
N0192107553 - National Research Register
Key Words
Pneumonia, paediatric, treatment, antibiotics

Introduction

Pneumonia is a common paediatric illness with 2.5 million cases annually in Europe[1], most commonly in the < 5 year age group (incidence 21-36/1000 in the developed world)[2,3]. Around 40% of cases require hospitalisation [2,3]. The clinician has to make management decisions regarding choice of antibiotic and mode of administration. The BTS guidelines for treatment of community acquired pneumonia in children [4] made a consensus recommendation regarding the use of IV antibiotics for those admitted to hospital but not based on evidence. It is not possible to differentiate viral and bacterial pneumonia by chest x-ray (CXR) or inflammatory markers [5,6]. Hence the clinician has to treat this group of children empirically with antibiotics.

There have been no randomised controlled trials in the developed world comparing administration of antibiotics by the oral and IV route for children unwell enough to require hospital admission. A study of pneumonia in children presenting to thirteen hospitals in the north of England[7] demonstrated that the majority are admitted (89% of 711 children) and 96% received antibiotics, 70% by the IV route. The percentage of children classed as having mild, moderate and severe pneumonia was 22, 19 and 59% respectively in this study.

The aim of this study was to ascertain whether therapeutic equivalence exists for treatment of community acquired pneumonia (CAP) by the oral and IV route. Since oral antibiotics are cheaper and more acceptable to families and clinicians, being a less painful and non-invasive treatment, an equivalence trial was deemed the most appropriate approach to this question as there is no need to demonstrate superiority.

Methods

Patients

The study was a multicentre randomised but non-blinded equivalence trial of oral versus IV treatment for pneumonia in previously well children. Children were recruited from 8 centres in England (Queens Medical Centre Nottingham, City Hospital Nottingham, Derby Children's Hospital, King's Mill Hospital Mansfield, Lincoln County Hospital, Heartlands Hospital Birmingham, New Cross hospital Wolverhampton and University Hospital North Staffordshire). All children admitted to hospital with pneumonia were eligible. Three inclusion criteria had to be met for pneumonia to be diagnosed: respiratory symptoms or signs, temperature of $\geq 37.5^0$c or a history of fever at home, and a radiological diagnosis of pneumonia (defined as a confluent area of consolidation agreed subsequently by two independent radiologists). The decision to admit and study eligibility was assessed by the admitting team. Exclusion criteria were wheeze, oxygen saturations < 85% in air, shock requiring > 20mls/kg fluid resuscitation, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy and age < 6 months. Treatment with oral antibiotics in the five days prior to admission, including amoxicillin, was not an exclusion criterion.

Procedure

Written informed consent was obtained prior to randomisation. A block randomisation sequence stratified by centre was produced using a random number generator. The sequence was accessed via the internet, therefore allowing concealment of allocation. Children were randomly assigned to oral amoxicillin (chosen in preference to oral penicillin due to the superior absorption [8] and palatability) or IV benzyl penicillin. Children in the IV group were changed to oral amoxicillin on discharge or sooner if the clinical team considered their improvement warranted this. Both groups completed a one week course of antibiotics in total. Doses were taken from 'Medicines for Children',2001[9], the most authoritative guide to paediatric drug doses at the time in the UK. Oral amoxicillin: 6 months to 12 years 8mg/kg three times a day;12-16 years 500mg three times a day. Benzyl penicillin IV: 6 months to 16 years 25mg/kg four times a day.

Admission investigations included, full blood count, C-reactive protein, blood culture and a viral throat swab or nasopharyngeal aspirate (for viral immunofluoresence and culture for respiratory syncitial virus, adenovirus, parainfluenzae and influenza A and B viruses). The protocol included as rescue treatment, in addition to amoxicillin or benzyl penicillin, oral erythromycin (in both treatment groups) or clarithromycin IV if oral medication was not tolerated. This was started at 48 hours if no clinical improvement was noted. Parents were telephoned two weeks following discharge and weekly thereafter until the child was judged by the parent to be back to normal (defined as not coughing more than prior to the pneumonic illness and energy levels back to normal).

Outcome Measures

The primary outcome measure was time from randomisation until the temperature had been less than 38˚C for 24 continuous hours **and** oxygen requirement had ceased (the latter only applicable to those children who required oxygen during the admission). It can be seen from the inclusion criteria that a temperature of >37.5^{o}C was chosen although the primary outcome measure is based on a temperature < 38^{o}C. Many

children would have been treated with anti-pyretics prior to presentation to hospital and therefore using a higher cut off would have unnecessarily excluded a proportion of children with pneumonia. The use of a temperature < 38°C for recovery was decided by a consensus group of senior clinicians prior to the start of the study. Secondary outcomes included time in hospital, complications (empyema, readmission, further courses of antibiotics), duration of oxygen requirement and time to resolution of illness. This was a pragmatic trial and the decision to change from IV to oral antibiotics and discharge home were at the discretion of the clinical team (ensuring children were not kept in hospital for longer than they would be in normal clinical practice).

Power calculation

With a 5% level of significance, 80% power and equivalence defined as no more than a 20% difference between treatments of the proportion meeting the primary outcome measure at any time, 98 children were required in each arm of the trial. The steering group and a focus group advised that more than a 20% difference could not be considered clinically equivalent.

Statistical Analysis

Since this was an equivalence trial the primary analysis was per protocol. Criteria for inclusion in the per protocol (PP) analysis were as follows: oral amoxicillin +/- rescue treatment for the oral group; for the IV group the child must have received at least one dose of IV benzyl penicillin. This was a pragmatic trial and some children left hospital before the primary outcome measure was met giving rise to censored data. Censored observations are observations for which, at the end of the study, the event of interest (time for temperature to fall below 38 degrees for 24 continuous hours and oxygen requirement to cease) has not occurred. There was a further small group of children (13/203 = 6%) with censored observations in whom the temperature did not go above 38°C in hospital. Survival analysis is the most appropriate technique to analyse these type of data[10]. Wellek's log rank test was used to analyse for equivalence [11] (SAS Package version 8.2). Therefore, for the primary outcome measure p values < 0.05 define equivalence. Equivalence was judged as a difference of no more than 20% between the proportions of children in the two treatment groups meeting the primary outcome measure. Therefore a p value of <0.05 indicates that there is no more than a 20% difference between the 2 treatments at any time. Other p values are for superiority. As these are multicentre data, a stratified analysis was carried out.

A second analysis of the primary outcome measure is also presented. This analysis assumes the primary outcome measure was met following discharge e.g. if a child was discharged after having a temperature less than 38°C for 18 hours, the primary outcome measure was assumed to have been met a further 6 hours following discharge making a total of 24 hours (provided the child did not re-present to hospital and the symptoms fully resolved at telephone follow up). Categorical data were analysed using a Chi-squared test. Continuous data were analysed using a T-test or Mann-Whitney U test depending on the normality of the data. Skewed data are presented as medians with 25th and 75th centiles. A data monitoring committee met half way through the trial to monitor adverse events and trial progress.

Results

Between September 2002 and June 2004, 252 children were randomised. Figure 1 shows the number of children who were eligible, randomised, excluded and analysed in the per protocol group. Demographic variables are shown in Table 1.

Table 1
Demographics and Clinical Variables (per protocol analysis)

Variable	Oral Treatment N=100	IV Treatment N=103
Sex	Male 53 (53%)	Male 55 (53%)
Age (years) (median and 25th-75th centile)	2.4 (1.5-5.4)	2.5 (1.4-4.7)
Number of children treated with oral antibiotics pre-admission	18 (18%)	14 (13.6%)
Number of days treatment with antibiotics pre-admission*		
< 2 days	14/18 (78%)	12/14 (86%)
2-5 days	0/18	2/14 (14%)
> 5 days	4/18 (22%)	0/18
Length of illness pre-admission in days (median and 25th-75th centile)	5 (2.5-7.0)	4.5 (2.0-7.0)
Admission observations: - (mean and 95% CI)		
Temperature	38.6 deg (38.4-38.8)	38.4 deg (38.2-38.6)
Pulse	151 (146-156)	149 (144-153)
Respiratory rate		
< 1 year	50 (45-61)	50 (45-61)
> 1 year	40 (37-43)	43 (40-46)
Oxygen saturation (in air)	95% (94-96)	95% (95-96)
Symptoms and signs on admission: -		
cough	89 (89%)	95 (92%)
recession	42 (42%)	51 (49.5%)
grunting	14 (14%)	25 (24%)
difficulty breathing	34 (34%)	33 (32%)
Investigations	Blood taken from 79/100 (79%) Throat swab or NPA taken from 55/100 (55%)	Blood taken from 89/103 (86%) Throat swab or NPA taken from 52/103 (50%)

White cell count $x10^9/l$ (mean and 95% CI)	19 (16.8-20.8)	18 (16.5-19.6)
Neutrophil count $x10^9/l$ (mean and 95% CI)	14 (12.3-15.9)	13.4 (11.9-14.9)
C-reactive protein mg/l (mean and 95% CI)	159 (128-190)	172 (144-199)
Blood culture	1 positive *(Streptococcus pneumoniae)*	3 positive *(Streptococcus pneumoniae)*
Viral throat swab or nasopharyngeal aspirate (NPA)	Positive 8/54 (15%) - 4 respiratory syncitial virus - 2 influenzae A - 1 adenovirus	Positive 7/52 (13%) - 5 respiratory syncitial virus - 1 influenzae A - 1 parainfluenzae

No significant difference seen between the 2 groups for white cell count, neutrophils or CRP.

* The oral antibiotics given prior to hospital admission included amoxicillin (11), cephalexin (2), co-amoxiclav (3), penicillin (4), erythromycin (7), clarithromycin (1) and trimethoprin (4)

Primary Outcome Measure

For the primary outcome measure all p values are for equivalence. Therefore a p value < 0.05 indicates that the null hypothesis (a difference >20% exists between the 2 treatments) has been disproved. As shown by the survival curves in Figure 2, the time for temperature to settle and oxygen requirement to cease for those needing oxygen was similar in the two groups (p=0.03 for equivalence, median time 1.3 days, 1.1-1.7 days 25^{th}-75^{th} centile and 1.2 days, 0.9-1.6 25^{th}-75^{th} centile in the IV and oral groups respectively). We also calculated the mean difference (and 95% confidence interval) in the primary outcome measure between IV and oral groups and this was found to be 0.3 hours (0.21, 0.40). Figure 3 demonstrates the same curves using the estimated time for temperature to settle in those children who were discharged before the primary outcome measure was met. Stronger evidence of equivalence was demonstrated (p=0.001, median time for temperature to settle 1.3 days in both groups).

A secondary analysis of the primary outcome measure was undertaken using only time for temperature to settle and excluding oxygen requirement. The median time for temperature to be <38 degrees for 24 continuous hours was 1.23 and 1.3 days respectively in the IV and oral groups (p=0.0002 for the per protocol analysis).

Time in hospital and oxygen requirement

The median length of hospital stay was significantly shorter in the oral group compared to the IV group (1.77 days, 1-2.2.0, 25^{th}-75^{th} centile compared to 2.1 days, 1.8-2.9 25^{th}-75^{th} centile respectively p<0.001). We also calculated the median of the differences and this was found to be 0.60 day (0. 15-1.13) (IV-Oral). During admission, 18/103 (17.5%) and 28/100 (28%) of children in the IV group and oral groups respectively required oxygen (p=0.07). The duration of oxygen requirement was significantly longer in the IV group (median 20.5 hours compared to 11 hours in the oral group p=0.04). Children randomized to IV treatment received a median of 6 doses, 4.7-7.5 25^{th}-75^{th} centile of IV benzyl penicillin before conversion to oral amoxicillin.

Protocol deviations and other antibiotic changes:

Oral group

Three children in the oral group (7 months, 15 months and 3 years) commenced oral amoxicillin and were subsequently changed to IV antibiotics (benzyl penicillin or cefuroxime) in view of increasing respiratory distress or oxygen requirement. One had Downs Syndrome and one was subsequently diagnosed with measles.

Table 2
Protocol deviations and complications

Group		Oral Group (n=126)	Intravenous Group (n=120)
A	Did not receive treatment per protocol	5 (see figure 1)	4 (see figure 1)
B	Received treatment per protocol but subsequently changed to a second antibiotic other than rescue treatment	3	7
C	Rescue treatment per protocol	6	8
D	Number of children in group B who were also in group C	1	6
E	Empyema requiring drainage	0	3
F	Further course of antibiotics following discharge	6	3

IV group

Seven children in the IV group were changed to other IV antibiotics due to ongoing fever. Three developed empyema (described below) and four had antibiotic changes (IV cefuroxime, ceftriaxone or cefotaxime) due to ongoing fever and worsening consolidation on CXR.

Empyema

Three previously healthy children, all in the IV group, aged 11 months to two years developed empyema requiring drainage. None had received antibiotics prior to admission. Fully sensitive *Streptococcus pneumoniae* was isolated from two of these children. In the third, no organism was identified. All made a full recovery.

Follow-up

Time to resolution of symptoms (defined as not coughing more than prior to the pneumonic illness and energy levels back to normal) was a median of nine days in both treatment groups. Eight children received a further course of oral antibiotics for ongoing cough between five and 28 days following discharge (six in the oral group and two in the IV group). All subsequently made a full recovery. One child in the IV group was readmitted to hospital 15 days following discharge with ongoing cough and new fever and received a second course of IV antibiotics.

Discussion

This is the first randomised controlled trial in children in the developed world to study oral versus intravenous treatment for children with radiologically confirmed pneumonia, treated in hospital. Our data show that oral amoxicillin and IV benzyl penicillin have equivalent efficacy for the treatment of pneumonia in previously well children. Oral treatment allowed children to go home sooner and avoided pain from cannulation. Both groups took a median of 9 days to recover.

Oral amoxicillin was chosen in preference to oral penicillin for a number of reasons. This was a pragmatic trial; most clinicians would choose amoxicillin over penicillin by the oral route due to its superior absorption and palatability[8]. Amoxicillin does have cover against Haemophilus which penicillin lacks. However since the introduction of Haemophilus influenzae Type b vaccine this has become a rare cause of pneumonia. Non-typable Haemophilus strains have never figured highly in aetiology studies[12,13].

Children in the IV group received oxygen therapy for a significantly longer period than those on oral treatment. Theoretically, by chance those randomly allocated to IV treatment could have been a group of children with more severe pneumonia. However the demographic variables suggest the groups were similar. (Table 1). A more likely explanation is the fact that they stayed in hospital for a longer period of time and so continued to have oxygen saturation monitoring. This may have biased the primary outcome measure towards the oral group. However, a secondary analysis of the primary outcome measure looking solely at time for temperature to settle also demonstrated equivalence.

In terms of complications, the three cases of empyema were all in children on IV therapy. Six children in the oral group as opposed to two children in the IV group received further courses of antibiotics following discharge. However of these six children in the oral group, two had sought further advice from the GP due to ongoing cough and the other four children visited the GP with an increasing cough plus new coryza +/- new fever.

Yield from blood culture at presentation was low as seen in other studies [12,14,15] and did not predict complications. Numerous studies have demonstrated that white cell count and c-reactive protein cannot be used to differentiate viral and bacterial pneumonia [6,12]. These investigations did not appear to influence management decisions in this study.

There have been no studies in the developed world comparing oral versus IV treatment for children with pneumonia. There has been one study comparing oral amoxicillin to a single dose of intramuscular penicillin [16]. No difference was seen between the two groups. However, this study enrolled children well enough to be treated as outpatients and therefore potentially a different population to the present study. Moreover IM penicillin is not used for children in the UK and follow up was only for 36 hours. Oral amoxicillin has been claimed to be effective for treatment of 'severe pneumonia' in the developing world but the cases were not radiologically confirmed [17,18]. This may have led to recruitment of children with non-pneumonic respiratory illness. In contrast our study was not stratified by disease severity but does have the major advantage that all cases analysed per protocol had radiological

changes confirmed by 2 independent masked consultant radiologists. The study by Addo-Yabo et al[17] demonstrated equivalence comparing oral amoxicillin and intramuscular penicillin for children with a clinical diagnosis of severe pneumonia (treatment failures were 19% in each group). This study is unlikely to change practice in the developed world due to a number of differences between the two populations. Notably, different antibiotic resistance patterns and immunization rates and the co-existence of other disease such as malaria, HIV and malnutrition. In an era of evidence based medicine, clinicians demand evidence that is directly applicable to the population of patients they treat. Hence studies from both the developing and developed world are needed.

A double blind randomised controlled trial would have been the gold standard for this study. However, it would not have been acceptable to cannulate half the children to receive only placebo and frequently re-cannulate them if IV access was lost before the child was discharged. The pragmatic nature of the study led to a number of children being discharged before the primary outcome measure was met. It would not have been ethical to keep children in hospital for a minimum period for the purposes of the study. It was also our aim to compare oral treatment to current IV practice, not a minimum number of doses specified for the purposes of the study. Time in hospital could have been used as the main outcome measure and would have been available on all participants but could have been biased by factors such as social circumstances, bed pressures and clinicians with different criteria for discharging children. As this was a pragmatic study, admission criteria were not applied and admission was at the discretion of the admitting team.

This study did not aim to look at aetiology which has been well documented in other studies [6,12]. The investigations in table 1 were baseline investigations, routinely carried out on children with pneumonia admitted to hospital in the participating centres. Children in whom a virus was isolated were not excluded, as many will represent a mixed infection [19] and all presented with consolidation. In this situation the clinician would initiate and continue to treat with antibiotics. Despite the exclusion of wheezy children it is accepted that some of the children within the study would have had viral pneumonia. It can be seen from the number of positive viral swabs that the numbers are small and more importantly balanced between the two groups.

Implications for future practice

The hospitals that took part in this trial represent a mixture of small and large district general hospitals and tertiary referral centres. There is no reason to believe that they admit a different population of children with pneumonia compared to other hospitals in the UK. Clinical coding demonstrated that admissions for children with pneumonia did not change during the trial period, suggesting stable admission practices.

We suggest that in countries like the UK with universal *Haemophilus influenzae type b* immunisation coverage and low rates of TB, all but the sickest children with pneumonia (i.e. those meeting our exclusion criteria) should be treated with oral amoxicillin. It is expected that the majority of children will still require hospital admission but for a shorter period to ensure oral medication is tolerated and temperature and respiratory distress are settling. Most importantly, children will be

spared the pain and distress which cannulation causes not only to them but also to their parents.

Conclusion

Oral amoxicillin is likely to be equivalent in the measured clinical outcomes to intravenous penicillin for the treatment of non-severe radiographic pneumonia in children admitted to hospitals in the UK. This non-blinded randomised controlled pragmatic equivalence trial addresses an evidence gap in the BTS guidelines for treatment of community acquired pneumonia in children [4]. Children will benefit from receiving a painless, non-invasive treatment. Although not reported in this study, there are also implications for reducing the direct and indirect costs of treating pneumonia in this population.

Figure 1
Consort Flow Chart

Figure 2
Survival curve for the time for the temperature to be < 38^{o}C for 24 continuous hours and oxygen requirement to cease in the 2 treatment groups (censored data, per protocol analysis)

Figure 3
Survival curve for the time for the temperature to be < 38^{o}C for 24 continuous hours and oxygen requirement to cease in the 2 treatment groups (no censored data, per protocol analysis)

We would like to thank the collaborating centres: City Hospital Nottingham, King's Mill Hospital Mansfield, Lincoln County General Hospital, Derby Children's Hospital, New Cross Hospital Wolverhampton, Heartlands Hospital Birmingham and University Hospital Stoke. The co-ordinating doctors at the collaborating centres (Dr H Clements, Dr D Thomas, Dr S Hartshorn, Dr C Groggins, Professor I Choonara, Dr N Ruggins, Dr J Anderson, Dr S Carter, Dr A Qureshi, Dr O Hamood, Dr W Lenney and Dr J Alexander). Also Graham Watson for the internet randomisation and Dr J Minford, Dr N Broderick and Dr J Sommers for kindly reporting the chest x-rays.

The guarantor of the paper is Professor Terence Stephenson.
There are no additional contributors.
The study protocol was reviewed and approved in all participating hospitals (multi-centre research ethical approval was given by the West Midlands Ethics Committee).
No authors have competing interests to declare.
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Figure 1

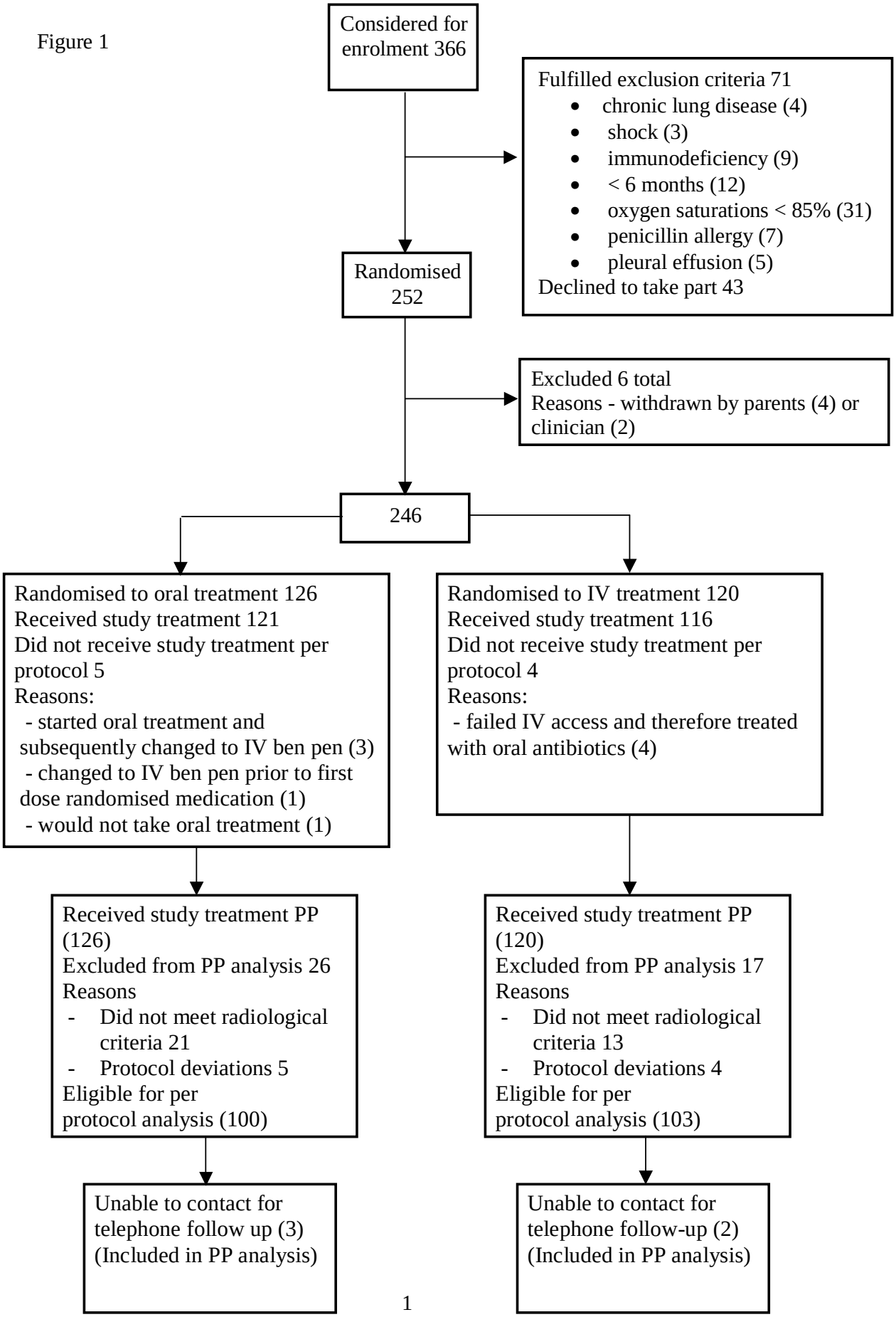
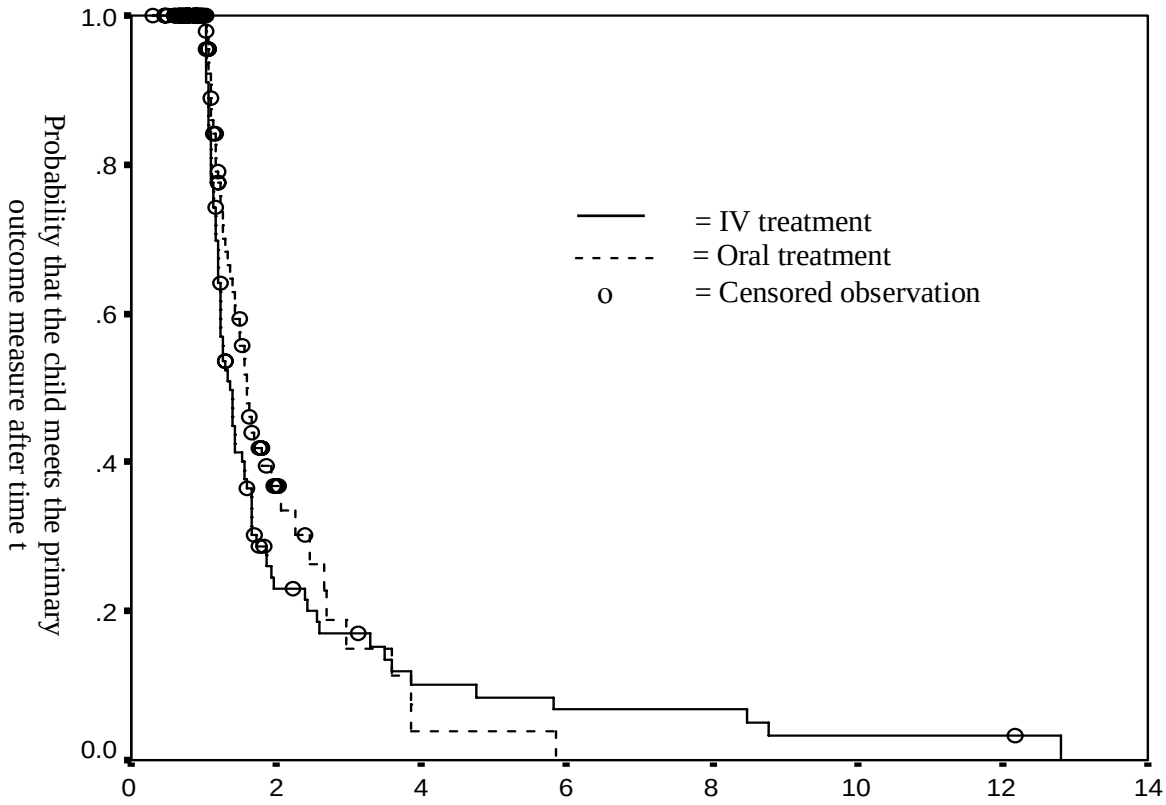


Figure 2

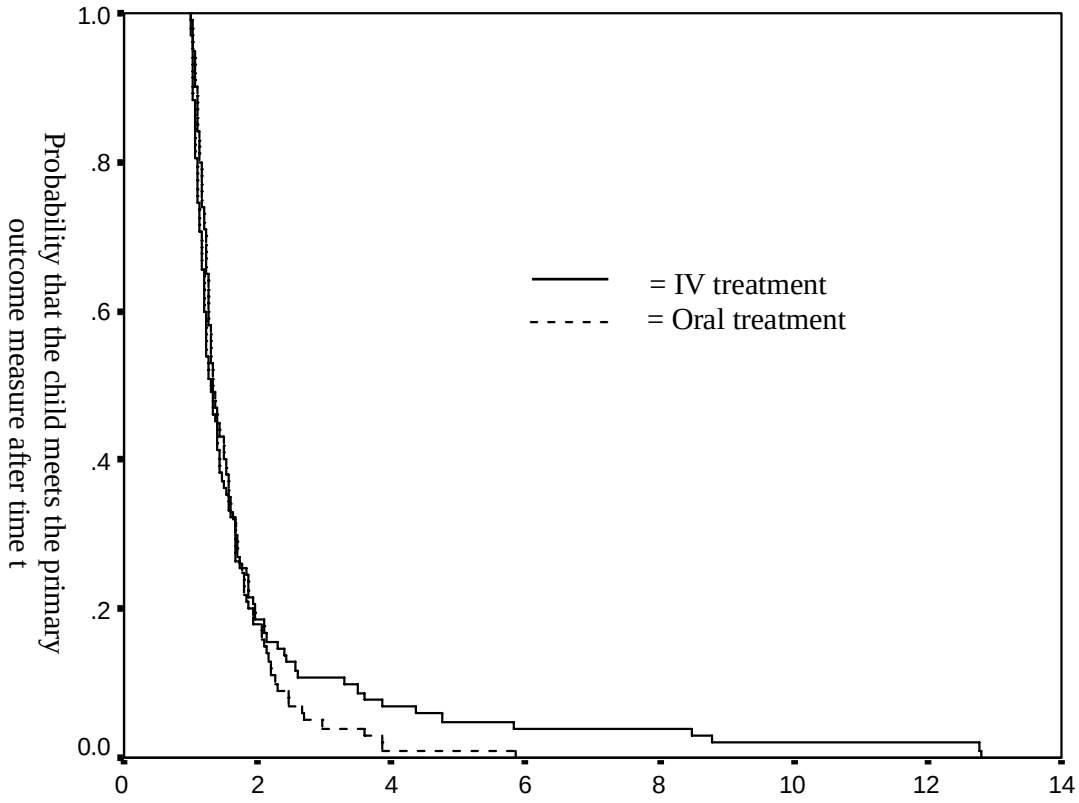
Survival curve for the time for the temperature to be < 38°C for 24 continuous hours and oxygen requirement to cease in the 2 treatment groups (censored data, per protocol analysis)



Per protocol analysis p = 0.031

Figure 3

Survival curve for the time for the temperature to be < 38°C for 24 continuous hours and oxygen requirement to cease in the 2 treatment groups (no censored data, per protocol analysis)



Per protocol analysis p= 0.001