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Oral *versus i.v.* antibiotics for community-acquired pneumonia in children: a cost-minimisation analysis

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ABSTRACT: Community-acquired pneumonia represents a high financial burden to healthcare providers. This manuscript seeks to estimate and compare the costs of treating children hospitalised with community-acquired pneumonia, with oral and intravenous antibiotics, thus determining which treatment is cost minimising.

A cost-minimisation analysis was undertaken alongside a randomised controlled non-blinded equivalence trial. 232 children (from eight paediatric centres in England) diagnosed with pneumonia, who required admission to hospital, were randomised to receive oral amoxicillin or *i.v.* benzyl penicillin. The analysis considered the cost to the health service, patients and society, from pre-admission until the child was fully recovered.

Oral amoxicillin and *i.v.* benzyl penicillin have equivalent efficacy. Children treated with *i.v.* antibiotics were found to have significantly longer in-patient stays (3.12 *versus* 1.93 days; $p<0.001$). *i.v.* treatment was found to be more expensive than oral treatment (£1,256 *versus* £769; difference £488; 95% CI: £233–£750), such that treatment of community-acquired pneumonia with oral amoxicillin would result in savings of between £473 and £518 per child (€545 and €596 per child) admitted.

The findings demonstrate that oral amoxicillin is a cost-effective treatment for the majority of children admitted to hospital with pneumonia.

KEYWORDS: Cost-minimisation analysis, paediatric, pneumonia, treatment

Cost-of-illness (COI) studies document the high financial burden that community-acquired pneumonia (CAP) represents to healthcare providers [1–4]. It has been estimated that 5.6 million cases of CAP occur each year in the USA, leading to 1.1 million hospitalisations. The resulting economic burden of treating CAP (in both primary and secondary care) was estimated to be $US8 billion annually (1995 values) [1]. Similar analyses in the UK suggests that £440.7 million (1992/1993 prices) was spent treating 261,000 annual episodes of CAP; 32% of these episodes were in-patient stays, which accounted for 96% of the total direct costs of CAP [2].

These COI studies combine both paediatric and adult episodes and are, therefore, likely to overestimate the cost of treating an episode of CAP in children, given CAP in children is associated with less morbidity and mortality than in adults. One study has estimated that there would be some 10,475 paediatric hospital admissions for pneumonia in England and the cost to the British National Health Service (NHS) would be £5.5–£7.1 million per annum (2004/2005 values), increasing to £6.3–£8.2 million per annum when including all associated healthcare costs [5].

In addition to the burden on the healthcare system, there is the burden on the rest of society, including lost productivity for parents and a reduction in quality of life for both the children with CAP and their parents. It has been reported that mothers of children hospitalised with CAP lost an average of 4.2 working days and incurred considerable private expenditure [6].

Given the burden of CAP is substantial, combine this with limited health budgets and the current economic climate, it is necessary to consider alternative treatment strategies in order to alleviate some of this burden. There has been some research on different management and treatment approaches to CAP, specifically on the efficacy of short-course antibiotics [7, 8]; however, research which considers the cost-effectiveness of different approaches is scarce, especially with respect to paediatric CAP.

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The PIVOT trial was a randomised controlled equivalence trial that demonstrated therapeutic equivalence for oral amoxicillin and *i.v.* benzyl penicillin for the treatment of CAP in children unwell enough to require admission to hospital [9]. It specifically sought to address an evidence gap in the British Thoracic Society's guidelines for treatment of CAP in children [10]. Additionally, in light of the paucity of paediatric data (particularly for indirect costs) and the potential cost savings to be made if equivalence was demonstrated, it was considered important to undertake an economic analysis on the direct and indirect costs of treating CAP in children admitted to hospital. As this trial was designed to show equivalence, and both treatments were found to be equally efficacious, it is appropriate to undertake a cost-minimisation analysis (CMA) [11]. The present study presents a comparison of the direct and indirect costs of treating children with CAP with oral and *i.v.* antibiotics, and aims to establish which treatment is cost-effective.

MATERIAL AND METHODS

The economic evaluation was planned, funded and conducted alongside a multicentred non-blinded equivalence trial of oral amoxicillin and *i.v.* benzyl penicillin, the PIVOT trial. Full details of the trial can be found elsewhere [9] but, in brief, children (recruited from eight centres in England) with CAP, who required admission to hospital were randomised to receive either oral amoxicillin or *i.v.* benzyl penicillin. Children in the *i.v.* group were changed to oral amoxicillin on discharge or sooner if the clinical team considered their improvement warranted this; irrespective of their treatment both groups completed a 1-week course of antibiotics in total. Doses were taken from Medicines for Children (2001) [12], the most authoritative guide to paediatric drug doses at the time in the UK. Oral amoxicillin: age 6 months to 12 yrs, 8 $mg \cdot kg^{-1}$ three times a day; age 12–16 yrs, 500 mg three times a day. Benzyl penicillin *i.v.*: age 6 months to 16 yrs, 25 $mg \cdot kg^{-1}$ four times a day. For the purposes of the study, three inclusion criteria had to be met for pneumonia to be diagnosed: the presence of respiratory symptoms or signs; temperature of $\geqslant$37.5°C or a history of fever at home; and a radiological diagnosis of pneumonia. Exclusion criteria were wheeze, oxygen saturations <85% in air, shock requiring more than 20 $mL \cdot kg^{-1}$ fluid resuscitation, immunodeficiency, pleural effusion requiring drainage, chronic lung condition (excluding asthma), penicillin allergy and age <6 months. The study protocol was reviewed and approved in all participating hospitals, and multi-centre research ethical approval was given by the West Midlands Ethics Committee.

Measurement of outcome

The outcome measure in the clinical trial was time from randomisation until the temperature had been less than 38°C for 24 continuous hours and oxygen requirement had ceased (the latter was only applicable to those children who required oxygen during the admission).

Notably, one of the inclusion criteria was a temperature of $\geqslant$37.5°C, while the primary outcome measure is based on a temperature of <38°C. Given many children would have been treated with antipyretics before presentation to hospital and a higher cut-off point 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 before the start of the study

Perspective

The economic evaluation was conducted from a societal perspective; it considered the costs incurred to the health service and the patient's family, as well as the cost of lost productivity. The cost to the health service included costs incurred prior to admission to hospital, the cost of investigations and treatment in the hospital and post-discharge costs. The cost to the patient's family included the cost of childcare, travel and expenditure whilst the child was in hospital. The nature of CAP is such that the illness is short-lived, generally CAP lasts no longer than 2 weeks and, as such, the analysis did not require any discounting of future costs.

Measurement of cost

Resource use, attributable to the treatment and admission of the patients, was collected using a comprehensively designed data collection sheet. This was completed by attending physicians on presentation at hospital, as well as during the ward stay. Along with clinically relevant data, information on investigations, treatments and contacts with health professionals prior to admission were also collected. This prospectively collected data was subsequently supplemented with retrospective data. Parents were telephoned 2 weeks following discharge and weekly thereafter until the child was judged by the parent to be back to normal (not coughing more than prior to the illness and energy levels returned to normal), as time to resolution of illness was a secondary outcome in the trial [9]. During these follow-up telephone interviews, parents were asked how often they visited the hospital to see their child, whether they stayed with their child, how much time off work this involved and whether additional childcare was required. Parents were also asked to estimate the expenditure they incurred (food, phone calls, parking) whilst in hospital and whether they were able to recoup any of these expenses.

Use of health services (primary care visits, in-patient hospital stays, outpatient hospital visits and telephone advice) was valued using publicly available sources [13–15]. The cost of investigations was determined locally from the main study centre; while the British National Formulary [16] was used to calculate the cost of antibiotics. Direct patient costs, specifically transportation expenses, were calculated using a route planner (to calculate the distance travelled) [17] combined with an estimate of motoring costs per mile [18]. Where parents indicated that a taxi or bus was used, the actual cost of this was used. The value of lost productivity, that is time away from employment, was estimated by using gender-specific average earnings [19]. Table 1 presents the unit costs employed in the evaluation, expressed in year 2002 prices pounds sterling (£).

Statistical analysis

Unit costs were combined with resource use information to obtain a cost per child with CAP. The primary analysis compared the total cost of each intervention; however, results for each individual cost component are also presented and compared. Average costs are presented, as are the mean differences in cost. The cost data are skewed and as such bootstrapped and bias-corrected 95% confidence intervals of

TABLE 1 Unit costs

Resource	Unit cost £	[Ref.]
GP visit	20	[13]
GP telephone advice	23	[13]
NHS walk-in centre visit	30.58	[14]
NHS Direct telephone call	15.11	[15]
A&E visit	75	[13]
A&E telephone call[#]	86.25	See footnote
Ambulance journey	201	[13]
Paediatric in-patient stay (per diem)	398	[13]
Chest radiograph	30	Local sources
Full blood count	3	Local sources
C-reactive protein[¶]	4	Local sources
Viral throat swab	13	Local sources
Nasopharyngeal aspirate	13	Local sources
Blood culture	33	Local sources
Amoxicillin	1.14 per 100 mL[f] 1.79 per 100 mL[##] 1.84[¶¶]	[16]
Benylpenicillin	0.42 per 600 mg vial	[16]
Cannulation[+]	7.63	Local sources
Mileage[§]	0.40	[18]
Lost income	Gender/job specific	[19]

Data are presented in £ sterling (2002 prices). [#]: estimated by applying the same conversation factor from general practitioner (GP) visits to GP telephone advice to accident and emergency (A&E) visits; [¶]: cost ranges £1–£8, depending on whether the test is requested alone or in combination with other tests, this was not known, so the median value was taken; [+]: total cost of cannulation (including the venflon, gloves, splints and bandage); [§]: average cost; [f]: 125 mg per 5 mL dose of oral suspension reconstituted in water, as paediatric dose is dependent of weight and/or age; [##]: 250 mg per 5 mL dose of oral suspension reconstituted in water; [¶¶]: 500 mg capsules (21 per pack).

the mean cost differences between groups are presented [20]. Given that the economic evaluation was conducted alongside an equivalence trial it is appropriate to conduct the analysis as per protocol (PP). However, an intention-to-treat (ITT) analysis is also presented for comparison. Statistical analysis used SPSS (version 13.0; SPSS, Chicago, IL, USA) and STATA (version 9; Stata Corporation, College Station, TX, USA).

Sensitivity analysis

The effects of changing key assumptions on the mean cost differences were undertaken by way of univariate sensitivity analysis [21]. These variations included increasing and decreasing by 10% the cost of treatment: that is the cost of an in-patient stay, the cost antibiotics and the accompanying cost of cannulation, as well as increasing and decreasing by 10% the total cost of treatment.

As this was a multicentred trial and variations in resource use (particularly in-patient stay) are expected across centres, regression analysis was used to control for any heterogeneity. A regression equation was employed, whereby the total cost was explained by the treatment arm, length of stay, baseline health status, prior healthcare attendance, age, sex and centre. Due to the large number of explanatory variables, a (backward) stepwise approach was used, whereby variables were removed if a significance level of 0.2 was not achieved.

Attempts were also undertaken to quantify potential cost savings and the budgetary impact of alternative treatment regimes, using the findings of two epidemiological papers [5, 22]. A study of 13 hospitals in the north-east of England over a period of 12 months found that 711 children with pneumonia presented to a paediatrician and 89% were admitted [22]. The authors further found that 501 children were given *i.v.* antibiotics: 70% of all children with CAP. Additionally, a separate study has estimated that there were 113 admissions for pneumonia per 100,000 children, and given the number of children in England (9.27 million as recorded in the 2001 census) this equates to 10,475 hospital admissions per year [5].

RESULTS

Between September 2002 and June 2004, 252 children were randomised to receive either oral or *i.v.* treatment for CAP. Six children were subsequently withdrawn by either their patients or clinician and a further 14 did not have complete resource data required for this economic analysis, such that the ITT analysis included 118 children who received oral amoxicillin and 114 who received *i.v.* benzyl penicillin. The PP analysis included 97 children in the oral group and 101 in the *i.v.* group.

Although the sample is slightly different from that reported in the clinical trial paper [9], the characteristics of the patients are similar and, importantly, comparable across treatment groups.

The trial found that oral amoxicillin and *i.v.* benzyl penicillin have equivalent efficacy, there was no significant difference for the time for temperature to settle and oxygen requirement to cease (for those requiring oxygen) between the two groups ($p=0.031$ for equivalence, median (interquartile range) time 1.3 (1.1–1.7) days, and 1.2 (0.9–1.6) days in the *i.v.* and oral groups, respectively). Further analysis, including those children who were discharged before the primary outcome measure was met, presented stronger evidence of equivalence ($p=0.001$, median time for temperature to settle 1.3 days in both groups) [9].

Table 2 presents resource use data for both groups of children for the PP sample. Most children (81%) consulted a general practitioner prior to presenting at hospital, while the majority of the remainder (31 out of 38 children) presented at an accident and emergency department. Those randomised to receive *i.v.* antibiotics spent significantly longer in hospital (average (range) 3.12 (0.58–18.14) days) than those who received oral antibiotics (1.93 (0.38–7.00) days) (note that the median value is also significantly higher in the *i.v.* group, that is the average is not merely a reflection of the large and skewed range). As a consequence of this, parents of children treated with *i.v.* antibiotics were found to take significantly more time off work (4.13 *versus* 2.84 days; $p=0.038$) and make a greater number of journeys to the hospital (11.94 *versus* 8.86 journeys; $p=0.038$).

These significant differences in resource use are comparable with the differences in mean costs. Table 3 presents the average cost of each intervention in terms of pre-admission, investigations, treatments, post discharge, and in aggregate for the health service and family, as well as the average total cost

TABLE 2 Resource use per protocol sample

Resource	*i.v.*	Oral	p-value#
Subjects n	101	97	
Pre-admission			
GP visit	1.34±0.98	1.29±1.01	0.735
GP telephone advice	0.13±0.44	0.16±0.45	0.567
NHS walk-in centre visit	0.02±0.14	0.05±0.27	0.291
NHS Direct telephone call	0.25±0.57	0.20±0.42	0.473
A&E visit	0.39±0.60	0.41±0.70	0.778
A&E telephone call	0.00±0.00	0.01±0.10	0.309
Ambulance transportation	0.09±0.29	0.13±0.34	0.317
Admission			
Investigations			
Chest radiograph	1.00±0.00	1.00±0.00	n/a
Full blood count	0.98±0.14	0.97±0.17	0.620
C-reactive protein	0.48±0.10	0.47±0.12	0.477
Viral throat swab	0.33±0.47	0.39±0.49	0.343
Nasopharyngeal aspirate	0.19±0.39	0.15±0.36	0.535
Blood culture	0.86±0.35	0.90±0.31	0.446
Treatment			
Amoxicillin doses	15.09±2.79	21.00±0.00	<0.001
Benylpenicillin doses	7.65±3.75		
Cannulation	1.30±1.07		
In-patient stay days	3.12±3.09	1.93±1.22	<0.001
Post-discharge			
GP visits	0.02±0.14	0.08±0.40	0.139
A&E visits	0.01±0.10	0.01±0.10	0.977
Time off work days	4.13±5.38	2.84±2.96	0.038
Journeys to and from hospital	11.94±10.32	8.76±6.10	0.009
Miles per journey	5.93±6.43	5.95±4.85	0.979

Data are presented as mean±SD, unless otherwise stated. GP: general practitioner; NHS: National Health Service; A&E: accident and emergency department. #: p-values of a significant difference in mean resource use were calculated using an independent samples t-test.

to society, for the PP analysis. The average cost of the interventions differ significantly in terms of the cost of treatment: *i.v.* is £488 more expensive than oral antibiotics, such that consequently *i.v.* antibiotic treatment (despite having lower costs pre- and post-admission and less costly investigations) is significantly more costly to the health service and to society as a whole, £473 and £518 respectively. The ITT analysis presented in table 4 shows a similar significant average cost difference, £380 for the health service and £420 for society as a whole. Collectively, these results suggest that treatment of CAP with oral amoxicillin would represent a societal (health service) cost saving per child admitted of between £420 (£379) and £518 (£473).

The cost of an in-patient stay makes the greatest contribution to the total cost of care, and unsurprisingly, varying this cost by 10% has the greatest sensitivity. Increasing (decreasing) the cost of in-patient care by 10% increases (decreases) the health service mean cost difference to £521 (£426). Varying the other treatment costs has a minimal effect.

The regression analysis (data not presented) found that while the length of stay dominated the total cost estimation, there was still some treatment effect not explained by this. In addition, those patients who had more visits to a general practitioner prior to admission had a lower cost, while those patients who made more calls to NHS Direct (a UK-based telephone helpline) had higher costs. Interestingly, one centre appeared to be different from the lead centre, whereby patients at one hospital incurred higher costs.

The budgetary impact analysis suggests that if 70% of all admissions for CAP are treated with *i.v.* antibiotics, but instead could be treated as effectively with oral antibiotics, then this would amount to a cost saving of £3.47 million (£4.17 million, 2007/2008 prices) [23] to the health service, or £3.80 million (£4.56 million, 2007/2008 prices) to society as a whole (using the per protocol cost difference).

DISCUSSION

The PIVOT trial was the first randomised controlled trial in children in the developed world, to study oral *versus i.v.* treatment for CAP, who were unwell enough to require admission to hospital. The clinical trial found that oral amoxicillin and *i.v.* benzyl penicillin have equivalent efficacy with respect to the treatment of pneumonia in previously well children [9].

This economic analysis conducted alongside the PIVOT trial has found that the total cost of treating CAP was significantly lower in the oral group compared to the *i.v.* group. As many other studies have shown the biggest component of cost associated with treating the illness is the cost of being in hospital [2]. Since the oral group were admitted for a significantly shorter period it is perhaps not surprising that the cost of treatment was lower in this group. Multivariate regression analysis, to control for heterogeneity, confirmed that length of stay dominates the cost estimation, but there was some influence of prior resource use (that is more GP visits prior to admission) lowering costs, which may be due to these children being in the later stages of their illness relative to others. Notably one centre incurred significantly higher costs than the lead centre; without further data we can only assume that this is a reflection of different clinical practice or a more severely ill group of patients.

In addition to estimating the healthcare costs of treatment, this is the first cost analysis to also estimate the indirect costs of treating CAP in children admitted to hospital (previous studies only quantified the burden and did not value it in monetary terms [6]). Parents were found to incur high costs (>£140) despite the relatively short hospital stay experienced by both groups of patients.

It is likely that these estimates may under-represent the total cost of treating CAP in children. A proportion of children in both groups would have been followed up in outpatients possibly with a repeat chest radiograph, although data were not collected on this aspect of care. While data were collected on the number of health contacts in the week prior to admission, it is possible that some children were unwell for more than a week and therefore had additional healthcare contacts.

TABLE 3 Cost and differences by cost category per protocol analysis

	i.v.	Oral	Mean difference (95% CI#)
Subjects n	101	97	
Cost pre-admission	80.70±78.12	91.42±88.59	-10.72 (-33.87–12.42)
Cost of investigations	71.90±14.69	73.36±13.87	-1.46 (-5.40–2.48)
Cost of treatment	1256.30±1235.61	769.73±487.06	487.57 (233.21–749.93)
Cost post-discharge	1.14±7.93	2.42±10.92	-1.28 (-3.93–1.37)
Cost to health service	1410.04±1244.18	936.94±509.74	473.10 (217.80–728.41)
Cost to families	187.07±220.72	142.39±224.79	44.68 (-17.37–106.73)
Total societal cost	1597.11±1353.43	1079.32±647.04	517.78 (222.57–813.00)

Data are presented as mean±SD £ sterling (2002 prices), unless otherwise stated. #: bootstrap estimation using 1,000 replications, bias corrected.

Therefore, it is likely that the estimated cost savings of £4.17 million to the NHS in England actually represents a minimum position. This finding also shows that previous estimations of the burden [5] considerably underestimate the actual burden; in part, due to the assumption that a hospital admission costs £150 per day, the true cost of a paediatric in-patient stay is over twice as much, nearly £400 [13]. Using this figure to update previous estimations [5], the annual cost of paediatric CAP in England (for all associated healthcare costs) is estimated to be between £13.5 million and £18.9 million (2007/2008 prices), such that a treatment regime of oral antibiotics has the potential to save between 20 and 30% of the cost.

There has been one previous paediatric study which estimated the costs of treating CAP in children [24]. They found that, following the introduction of a new management regime, length of stay decreased from a mean of 8.3 to 4 days. Mean total healthcare costs in the control group were £2,463 (1995/1996 prices) compared with £1,167 with the new protocol. They estimated savings, for the 45 patient in the study treated under the new protocol, of £58,000. Since these authors conducted this study, there has been a general trend towards shorter hospital admissions for children [25], hence the considerably short length of stays reported in our study.

A recent study in Italy compared therapeutic treatment practices for acute lower respiratory infections in children [26]. They found that oral antibiotic therapy, by itself, or a new pattern of administration, so-called ''switch therapy'', whereby antibiotics are administered by the parenteral route for 1 or 2 days and then switched to administration by the oral route, were both significantly less costly than treatment that used neither of these therapies. The main cost driver in this longitudinal observational study, as also reported in our study, was length of stay.

Given the cost savings that are reported are nearly entirely driven by reductions in length of stay, there may be some concern that the savings experienced in secondary care are instead incurred as costs in other areas of the health sector; that is, there is a shifting of burden from in-patients to outpatients or primary care (*e.g.* early discharge results in more follow-up outpatient visits or GP appointments). We found no evidence of different levels of resource use post-discharge and this has also been confirmed in a study which considered the optimal duration of oral antibiotic use [27]. These researchers compared short 3-day antibiotic therapy with standard 8-day therapy in hospitalised adults with CAP and found that while some of the lower costs of the short duration therapy were offset by higher costs in primary care, ultimately there was no significant difference in costs between the two treatment groups, thus no evidence of a substitution effect.

The strength of the results reported here are, in part, due to the fact that the economic evaluation was undertaken prospectively alongside an equivalence trial. Equivalence studies are rare; most

TABLE 4 Cost and differences by cost category in intention-to-treat analysis

	i.v.	Oral	Mean difference (95% CI#)
Subjects n	114	118	
Cost pre-admission	82.71±79.92	87.24±83.95	-4.52 (-25.80–16.75)
Cost of investigations	71.78±14.76	72.39±14.72	-0.61 (-4.16–2.94)
Cost of treatment	1237.06±1183.62	851.25±799.31	385.80 (140.90–630.71)
Cost post-discharge	1.01±7.47	2.16±10.07	-1.15 (-3.42–1.11)
Cost to health service	1392.57±1193.81	1013.05±807.42	379.52 (118.32–640.72)
Cost to families	176.86±215.48	136.87±207.46	39.99 (-14.82–94.80)
Total societal cost	1569.43±1301.67	1149.92±891.97	419.51 (134.61–704.41)

Data are presented as mean±SD £ sterling (2002 prices), unless otherwise stated. #: bootstrap estimation using 1,000 replications, bias corrected.

pharmaceutical trials seek to establish superiority in order to claim an advantage over competitors and thereby justify a higher price [28]. CMA are also becoming rare; this is due to a growing understanding of what deems treatments to be equal [11]. Notably, equivalence was established in the trial using clinical outcome measures, yet it is likely that quality-of-life measures, like the EQ5D [29] or HUI [30] would have found that oral antibiotics are more effective than *i.v.* treatment, given that oral treatment is non-invasive and children can return home sooner. Studies which have estimated parental quality of life, report that the greatest reduction was experienced by parents whose children were hospitalised [6].

Oral amoxicillin has been previously shown to be equivalent to *i.v.* benzyl penicillin for the treatment of non-severe pneumonia in children admitted to hospitals. This study reports that oral amoxicillin is also a cost-effective treatment for these children. As a result, there is considerable potential to achieve cost savings (for both the health service and society) if all but the sickest children hospitalised with pneumonia are treated with oral antibiotics instead of *i.v.* antibiotics, as treatment with oral amoxicillin results in a shorter in-patient stay.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

A statement of interest for H. Vyas can be found at www.erj.ersjournals.com/misc/statements.dtl

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