Multicenter Observational Study to Assess the Safety of Outpatient Treatment of Severe Pneumonia with Oral Amoxicillin in Children aged 3 to 59 months: A Pilot Safety Study

(EGYPT FINAL REPORT)

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Background

Acute respiratory illnesses (ARI) are the leading cause of childhood mortality in developing countries, including Egypt. In order to reduce ARI related mortality, WHO has developed standardized case management guidelines for the treatment of ARI in children. A recent review published in the Lancet has shown that there has been a reduction of up to 36% in ARI related mortality in communities where these standardized case management guidelines have been implemented.

Despite the reduction in ARI related mortality, there is a continuous ongoing effort to further improve these case management guidelines. A trial carried out in 1991-92 showed that children with severe pneumonia responded better to oral amoxicillin as compared to oral cotrimoxazole. On the basis of this finding a large multi-country multicenter trial was conducted in which children with severe pneumonia were randomized to receive either oral amoxicillin or injectable penicillin.

The results of this trial (APPIS) have been published in the *Lancet* (vol 364, 1141-1148) and show that oral amoxicillin is equivalent to injectable penicillin for the treatment of severe pneumonia as defined by current ARI case management guidelines. This work represents a major breakthrough which will likely have huge policy implications worldwide. Before this finding is translated into changes in Integrated Management of Childhood Illness (IMCI) case management guidelines, ARI experts have requested community-based trials which demonstrate the safety and efficacy of this intervention.

Objectives

This study attempted to answer this question by assessing the safety and efficacy of outpatient treatment of severe pneumonia with oral amoxicillin in children aged 3 to 59 months. This multicenter study was carried out in six centers, including Egypt, Bangladesh, Bolivia, Brazil, Ghana, and Vietnam.

Methodology

In the Egyptian chapter of the study, the study was approved by the Faculty of Medicine of the Suez Canal University Ethical Review Boards (IRB). The study team recruited 237 children diagnosed with severe pneumonia and eligible for outpatient management were treated with oral amoxicillin for 5 days administered at home. WHO-defined severe pneumonia (cough with lower chest indrawing) was used for recruiting the study sample. Enrollment in the Egyptian study site was completed in the period between November 2005 and July 2006. All children were monitored very closely at home by trained health care workers. Monitoring included physical assessment and in the case of deterioration appropriate changes in the treatment regimen, including referral to Suez Canal University Hospital was made. Treatment was changed only if any pre-defined signs of deterioration were present at the time of follow-up. The objectives of the study were to assess the treatment failure rate at day 6 and day 14 and compare it to the treatment failure rates obtained in the APPIS trial. All children were assessed 14 days after enrollment. Data were entered into an Excel database and analyzed using SPSS.

Results

The study was conducted in seven rural primary health care centers in Ismailia governorate. It included 237 children aged 3-59 months of age, with mean age of 12.42 $\pm$ 10.05 months, presenting to the outpatient clinic of the participating centers with signs of severe pneumonia.

Clinical Cure rate with 5 days amoxicillin therapy at day 6 was 90.7%, while clinical cure rate at day 14 was 87.4%. Failure of therapy occurred more frequently in patients of low weight and in those with rapid respiratory rate (>50/minute). Loss to follow up occurred for 3 patients (1.3%), 3 patients were hospitalized (1.3%) and there were no deaths. Adverse effects occurred in 14 treated children (5.9%) in the form of mild diarrhea. Urine examination for antibiotics use before amoxicillin treatment showed that 15 out of 155 children (9.7%) received antibiotics, and there were no difference between cured or failed treated patients on antibiotics use before therapy.

Conclusion

It was concluded from the study that oral amoxicillin is effective and safe in treating pneumonia in children in ambulatory setting, when given for 5 days in a dose of 80-90 mg/kg/day in 2 divided doses.

Significance

The use of oral therapy for severe pneumonia will potentially lead to:

1) reduced mortality by reducing the progression to very severe pneumonia/disease;
2) reduced risk of needle-associated complications such as needle-borne infections;
3) minimization of the need for referral or hospitalization;
4) reduction of pressures on inpatient services;
5) decreased cost of delivering treatment; and
6) reduced transport, food and lost income costs for the family.

Results of this study reaffirm the results of the APPIS trial about the efficiency and safety of oral amoxicillin in treating children with severe pneumonia. These findings if proved to be compatible with findings presented in other centers of the multicenter study could have global implications for cost-effective management of childhood pneumonia.

1. STUDY BACKGROUND

1.1 Disease Burden and WHO Case Management of Pneumonia

Acute respiratory infection (ARI) is an important cause of morbidity and mortality in children under five years of age in developing countries. An estimated 2 million children under five years of age die each year due to acute lower respiratory infections (ALRI).[1,2] ARI is also a major cause of visits to outpatient and emergency departments and of admissions to hospital.[3-5] Bacterial infection plays a far greater role as a cause of pneumonia in children in developing countries than in developed countries. Pooled data from lung aspirate studies, mostly from developing countries reported a 55% isolation rate of bacteria.[6,7] The predominant bacteria were *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus*. Respiratory syncytial virus is also an important cause of acute respiratory infections in preschool children.[8,9] Emerging evidence indicates that *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* may cause pneumonia, but contribute substantially to cases of pneumonia above 5 years of age.[10-14] Data also shows that mixed viral and bacterial infections are common in children both in developing and developed countries[15-20], which need to be treated with antibiotics. More recently, data from a large vaccine trial suggests that *S. pneumoniae* probably has a major role in the development of pneumonia associated with viral infections.[21]

To address the high rate of mortality associated with ALRI, WHO launched a program for the control of ARI. The main objectives of the program were to reduce the child mortality and to rationalize antibiotic use. Currently standard ARI case management recommends that children with cough and normal breathing be treated as outpatients without antibiotics; those with tachypnea be given antibiotics on an ambulatory basis (non-severe pneumonia); while those with chest indrawing (severe pneumonia) be admitted to hospital and treated with parenteral antibiotics and supportive therapy.[22,23] For the severe pneumonia patients, the program recommends either injectable benzyl penicillin (penicillin G or crystalline penicillin) or ampicillin every six hours for at least three days. After the child has improved, it is recommended to switch to oral ampicillin or amoxicillin or to daily procaine penicillin injections to finish a course of at least five days. Vaccination against measles, pertussis, *H. influenzae* type b (Hib) and *S. pneumoniae* can help decrease the incidence and lessen the severity of respiratory infections. However, newer vaccines against respiratory infections such as Hib and pneumococcal conjugate vaccines are not widely available in developing countries.

1.2 Oral versus Injectable Antibiotic Therapy

There are inherent disadvantages associated with hospitalization and injectable therapy. First, the routine use of injectable antibiotics, either intravenously or intramuscularly substantially increases the cost of health care.[24] Second, it can increase the risk of transmission of HIV, hepatitis and other viral diseases transmitted through the use of contaminated needles.[25] Third, a number of children who are referred may not be able to get to the hospital[26] and do not receive treatment, placing them at risk of mortality. Fourth, hospitalization increases the risk of exposure to nosocomial pathogens that are increasingly difficult to treat due to antimicrobial resistance.[27,28] Furthermore, the rationale for a parenteral antibiotic is not fully established. Injectable therapy is chosen because of the

perception that it is more efficacious in the treatment of severe pneumonia rather than because of the children's inability to tolerate oral medication.

To overcome these disadvantages of hospitalization and injectable therapy recent research has looked at the potential use of oral treatment for severe pneumonia. In a study conducted in Pakistan, secondary analysis showed that oral amoxicillin was effective in 90% of bacteremic children with a clinical diagnosis of severe pneumonia.[29] The next step was to evaluate that severe pneumonia could be treated effectively and safely with oral amoxicillin. APPIS, the Amoxicillin Penicillin Pneumonia International Study, was a large open label equivalency randomized controlled trial comparing injectable penicillin versus oral amoxicillin,[30] at tertiary care centers in 8 countries. Children aged 3-59 months with severe pneumonia were hospitalized for 48 hours and, if improved, discharged with a 5-day course of oral amoxicillin. 1702 children were randomized to receive either oral amoxicillin (857) or parenteral penicillin (845) for 48 hours. Treatment failure was 19% in each group after 48 hours of therapy. Relapse between 5 and 14 days occurred in 45/1375 (3.4%) and 65/1330 (4.8%) of the children, respectively. Predictors of treatment failure included age <12 months, respiratory rate more than 70 per minute, and oxygen saturation <90% using a pulse oximeter at baseline. Injectable penicillin and oral amoxicillin were found to be equivalent in the treatment of severe pneumonia in this study.

1.3 Management of Pneumonia in HIV Exposed and Infected Subjects

In many parts of the world HIV infection is a major health problem in infants and children.[31] The infectious sequelae of advanced immunosuppression among these children are well-established. In APPIS,[30] children ill with severe pneumonia and HIV infection had a higher failure rate when treated with the standard WHO treatment of parenteral penicillin or an equivalent dose of oral amoxicillin compared with HIV uninfected children. It was concluded that HIV infected and exposed children with severe pneumonia failed WHO-standard treatment (or equivalent) at 2 and 14 days more often than the HIV uninfected children and this was especially true of the infants. WHO convened a meeting of experts, which recommended that in high HIV prevalent areas children 2-59 months of age suffering from severe pneumonia receive cotrimoxazole therapy.[32] In light of the above findings, in this study HIV exposed or infected children will not be enrolled. We have chosen to perform this study in HIV low prevalent areas, including Bolivia, Ghana, Bangladesh, Vietnam, Brazil and Egypt as HIV seroprevalence is low and we did not expect many children to be HIV infected.

1.4 Rationale for treating severe pneumonia at home with oral amoxicillin

In a recent set of articles addressing the child survival issues, ARI case management was cited as an evidence based intervention that could significantly reduce child mortality.[91] One of the targets for the 'Millennium Development Goals' set by international community is to achieve a two-third reduction in mortality in children under 5 years of age by 2015.[92] Community health workers (CHW) can be trained to assess sick children for signs of pneumonia; select appropriate treatments; administer the proper dosages of antibiotics; counsel parents on how to follow the recommended treatment regimen and provide supportive home care; and follow-up with sick children.[93] It is recognized that community acquired non-severe pneumonia is rarely associated with mortality if managed promptly with appropriate treatment.[66,57,59,94] Deaths occur when the pneumonia

progresses to severe or very severe categories. It is envisaged that providing training and support to CHWs in pneumonia case management will prevent deaths through early recognition and management of pneumonia, because some cases will progress to severe pneumonia and will die if not referred in time or where referral is not possible.

In summary, the potential benefits of oral therapy for severe pneumonia include: 1) reduced mortality by reducing the progression to very severe pneumonia/disease; 2) reduced risk of needle-associated complications such as needle-borne infections; 3) minimization of the need for referral or hospitalization; 4) reduction of pressures on inpatient services; 5) decreased cost of delivering treatment; and 6) reduced transport, food and lost income costs for the family. The major public health benefit of effective oral therapy of severe pneumonia at a community level would be to improve the availability of treatment to potential beneficiaries.

As a first step to management of severe pneumonia with oral amoxicillin in the community, current evidence from hospital based controlled trials points to efficacy of oral amoxicillin in severe pneumonia as a 'proof of principle'. When these findings were shared with a panel of experts brought together by WHO, the group felt that the programmatic implementation of home-based therapy for severe pneumonia would require more evidence.[58] However, they recommended that the intervention should be tested in a public health setting before it can be considered for inclusion as a generic treatment guideline for community management of severe pneumonia. If proven safe and effective, it would then provide a solid evidence base for community management of severe pneumonia. This was identified as a priority research area by that expert consultation and recommended that this question should be answered as soon as possible. Based on these findings and the issues mentioned above, it is proposed that WHO defined severe pneumonia be treated with oral amoxicillin at home and that those children should be followed up closely.

1.4.1 Oral amoxicillin

Amoxicillin is a bactericidal antibiotic, which is effective against *S. pneumoniae* and *H. influenzae.*[33] Amoxicillin is also active against up to 70 percent of *E. coli*. Group A and B streptococci and *L. monocytogenes* are also susceptible.[23,33] Amoxicillin is well absorbed after oral administration. Peak plasma concentration is reached after 2 hours and it is 2 to 2.5 times greater for amoxicillin than ampicillin after oral administration of the same dose.[33] An average of 4μ/ml are reached after 250 mg dose.[33] Food does not interfere with absorption. Effective concentration of orally administered amoxicillin is detectable in plasma for twice as long as oral ampicillin, because of more complete absorption.[33] Amoxicillin may be cross allergenic with other penicillins and in sensitized patients may evoke any of the hypersensitivity reactions that are caused by benzyl penicillin.[23] Rashes are more common with amoxicillin as compared to penicillin, but appearance of rash does not represent true penicillin hypersensitivity.[23] An urticarial or macular rash may appear 8-10 days (range 4-11 days) after the start of therapy. Prevalence of adverse effects has been reported in 0.7 to 10 per cent cases. Gastrointestinal side effects like diarrhea but also nausea and vomiting may follow oral administration. Diarrhea is rarely serious enough to require a change of therapy.[23] Anaphylaxis has most often been reported after injectable penicillin and the anaphylactic reactions have been reported from 0.004 to 0.04 per cent cases.[33]

1.4.2 Dosage and duration of therapy for amoxicillin

The objective of pneumonia treatment is to achieve a cure using a safe and effective antibiotic in an appropriate dose and duration. Decisions about dosage regimens are based on pharmacodynamics/pharmacokinetics of the antibiotic and its ability to inhibit bacteria by maintaining drug levels. Most treatment guidelines recommend 7-10 days of antibiotic therapy for the management of community acquired pneumonia in children based on custom and practice instead of evidence.[9,34,35]

Traditionally penicillin has been used to effectively treat *S. pneumoniae* infections. In recent years increasing reports of antimicrobial resistance have threatened this effectiveness,[36] but fortunately there is no evidence of bacteriological failure of penicillins active against resistant organisms.[37] Previous antibiotic use and longer duration of treatment are considered two of the most important factors in the selection of antimicrobial resistance.[38] Studies have identified recent antibiotic use as a risk factor for carrying resistant pneumococci[39-43] and having invasive infection with resistant pneumococci.[44,45] A longer treatment for more than 5 days with a beta lactam antibiotic was associated with increased risk of penicillin non-susceptible pneumococcal carriage.[46]

A short course of high dose antibiotic has been suggested as an intervention to reduce the spread of antimicrobial resistance.[47-49] Shorter courses would reduce the patient's exposure to antibiotic selective pressure and may reduce use in community, which is related to the antimicrobial resistance incidence. It has been shown that by reducing antibiotic use, reduction in antimicrobial resistance can be achieved.[50,51] Clinically shorter course of 4-day antibiotic therapy has been shown to be equally effective versus 7-day antibiotic therapy in children aged 3 months to 15 years with pneumonia, sepsis-like infections, or other common acute infections warranting hospitalization and parenteral antimicrobials. The clinical outcomes were similar between the two groups.[52-53]

The American Academy of Pediatrics recommends empiric treatment of acute suppurative otitis media with high dose amoxicillin (80-90 mg/kg per day), mentioning that based on drug concentrations and in vitro activity, no currently available oral antibiotic has better activity than amoxicillin against resistant *S. pneumoniae*.[54] A higher dose achieves drug concentrations that inhibit non-susceptible strains for a large proportion of the dosing interval.[55] This was documented by a study, which found the risk of penicillin-non-susceptible as well as cotrimoxazole non-susceptible pneumococcal carriage was significantly lower in the higher dose 5-day amoxicillin group in comparison with the standard dose 10-day group.[56] A shorter course of 3-day amoxicillin therapy also resulted in lower cotrimoxazole- non-susceptible pneumococcal carriage versus 5-day therapy,[57] whereas, another study found a higher proportion of non-susceptible *H. influenzae* carriage with 5-day as compared to 3-day cotrimoxazole therapy.[58] A shorter course of antibiotic has other benefits. It results in better adherence with the treatment of pneumonia.[56,57,59] It has been shown to be more acceptable to patients and their caretakers.[60,61] Furthermore, it reduces therapy costs.[24]

1.4.3 Frequency of amoxicillin administration

Traditionally amoxicillin has been used thrice daily. The more frequent amoxicillin dosing may lead to non-adherence. A study that compared the pharmacokinetics and levels of oral amoxicillin 15 mg/kg/dose thrice daily with the 25 mg/kg/dose twice daily regimen in children ages 3 to 59

months with pneumonia reported that the serum levels with twice daily amoxicillin were higher than thrice daily regimen.[62] They however did recommend that a higher twice daily dose would be better for treatment. Other studies have also reported twice daily amoxicillin to be a feasible alternative for thrice-daily dosing.[63-66] An expert consultation convened by WHO recommended using twice daily oral amoxicillin instead of thrice daily regimen for treatment of pneumonia.[58]

Thus, for this study we used antibiotic therapy for 5 days. Oral amoxicillin was used in 80-90 mg/kg per day divided into two doses.

1.4.4 Comparative advantage of amoxicillin over other groups of antibiotics

In the treatment of pneumonia the infecting organism is almost never known at the initiation of treatment. The treatment is based on judgments about safety and efficacy of therapy. In low resource settings, one has to also consider the cost of therapy. Macrolides (erythromycin, clarithromycin and azithromycin) are a group of broad spectrum antibiotics. Erythromycin is usually bacteriostatic, and is most effective against aerobic gram-positive cocci and bacilli.[33] Azithromycin generally is less active than erythromycin against gram positive organisms and is slightly more active than erythromycin and clarithromycin against *H. influenzae*. Azithromycin has a very long half-life and 5 days of therapy is considered equivalent to 10 days of standard antibiotic therapy. [33] Macrolides are quite effective against *C. pneumoniae and M. pneumoniae.* Macrolide resistance among *S. pneumoniae* is associated with penicillin and 60% of the penicillin resistant *S. pneumoniae* are also macrolide resistant. [33] Macrolide antibiotics can be used if either mycoplasma or chlamydia pneumonia is suspected and they can be used as first line therapy in children above 5 years of age as mycoplasma is more common in that age group.[35] Clarithromycin and azithromycin are much more expensive than erythromycin and amoxicillin.

Cephalosporin classification is based on generations. The first generation has good activity against gram-positive bacteria, but relatively modest activity against gram-negative microorganisms.[33] The second generation cephalosporins have somewhat increased activity against gram-negative microorganisms.[33] The third generation cephalosporins are generally less effective against gram-positive organisms as compared to first generation cephalosporins, but more effective against gram-negative ones[33]. Fourth generation cephalosporins have particular therapeutic usefulness in treatment of infections due to gram-negative bacilli resistant to the third generation. Cephalosporins have variable susceptibility to β-lactamase.[33] None of the cephalosporins has reliable activity against penicillin resistant *S. pneumoniae.* All cephalosporins are more expensive than amoxicillin.

Thus amoxicillin is the first choice for oral antibiotic therapy in children under 5 years of age because it is effective against the majority of organisms that cause community acquired pneumonia in this age group, achieves high tissue levels, is well tolerated and is inexpensive.

1.4.5 Why do children with severe pneumonia need hospitalization?

Children are hospitalized for the treatment of severe illnesses like severe or very severe pneumonia for several reasons: 1) to provide and facilitate parenteral antibiotic therapy, which ensures antibiotic therapy and adherence; 2) to provide and facilitate supportive therapy including feeding,

fluids and general nursing care; 3) to identify clinical deterioration in children who may need further treatment like oxygen or bronchodilator therapy, or sometimes a change of antibiotic therapy.

Oral antibiotic therapy at home would be an excellent alternative and would probably improve the outcome for many of these children. But there are concerns that by doing so, some of the other advantages of hospitalization may be lost. Most worrying is the failure to identify those children who deteriorate and subsequently require oxygen and intensive care facilities, where available. However, provision of these facilities in the typical low-resource setting may not be optimal. Some other issues related to care seeking and access to care are discussed in Section 2.5.

1.4.6 Justification to include 3 -12 month children for home treatment with oral amoxicillin

Although in the APPIS study, infancy (< 12 months of age) was a predictor of treatment failure, we believe a more detailed evaluation of the APPIS data supports the safe inclusion of children under 12 months of age in this study of home management with oral amoxicillin therapy.[30] Specifically, there were 12 deaths that occurred in the APPIS study; 7 deaths by 48 hours, 0 deaths between 48 hours and 5 days and 5 deaths between 5 and 14 days. Table I shows the breakdown in deaths by age and the HIV prevalence of the study setting. Eight deaths occurred in settings of high HIV prevalence and 4 deaths occurred in lower HIV prevalence settings. There were 2 children (age 12 months and 13 months, respectively) in HIV low prevalent settings who died by 48 hours in the APPIS study. This data suggests that infants (< 12 months of age) in HIV low prevalent settings were at no greater risk of death in the APPIS study than were older children. The 4 infants (≤ 12 months of age) who died by 48 hours in the APPIS study were from the Durban, South Africa or Zambia study sites, sites noted to have high HIV prevalence and which would not be included in this study.

Table I—Deaths by age in months and high and low HIV prevalence study sites.

	HIV Prevalence		
Age (months)	**High**	**Low**	**Total**
3-5	3	1	**4**
6-11	4	1	**5**
12-59	1	2	**3**
Total	**8**	**4**	**12**

Second, further analysis from APPIS indicates that children < 12 months of age were no more likely to be classified as treatment failures at 48 hours due to progression to very severe disease (i.e. abnormally sleepy, inability to drink, convulsions, received another antibiotic, hypoxemic) than were children ≥ 12 months of age (6% vs. 6% of all children in these age groups). In APPIS, children < 12 months were more likely to have persistence of lower chest wall indrawing at 48 hours than were children ≥ 12 months of age (89% vs. 53%), which in the APPIS study qualified them as a treatment failure, but would not in this home management study. With the frequency of home follow-up proposed in this study, we believe that somewhat prolonged persistence of lower chest wall indrawing without disease progression would introduce little to no additional risk to these children. Additionally, approximately half of these children, in both age groups, were noted

to be wheezing at the 48 hour evaluation, suggesting they were experiencing reactive airway disease or asthma

1.4.7 Justification to include children with RR > 70 and O_2 Sat < 90% in the trial

In the APPIS study, age less than 12 months, respiratory rate greater than 70 and oxygen saturation less than 90% were equal predictors of treatment failure in both the group which received standard (intravenous) therapy and the group which received oral amoxicillin at the 48 hour assessment. Since these predictors were no higher in the intervention group than in the standard therapy group, they imply that there exists an independent reason for this finding, not the difference in antibiotic therapy. The data from the APPIS study suggests that many children in APPIS had asthma, reactive airway disease or probable viral bronchiolitis which have a particularly high incidence in children under one year of age. It is expected that they would continue to have increased respiratory rates and lower oxygen saturations at 48 hours even when being treated for pneumonia. Unlike in APPIS, in this study, persistence of lower chest indrawing at 48 hours does not constitute a treatment failure and this study attempts to more stringently exclude those children with possible asthma and reactive airway disease from entry in the study. We will accomplish this by excluding children with known prior episodes of asthma, three or more prior episodes of wheezing and lower chest indrawing that resolves after three doses of bronchodilator therapy. More importantly, mortality or clinical deterioration requiring a change in antibiotic, were no greater in children less than 12 months or in those with persistent lower chest indrawing in the APPIS study. Finally, with regard to programmatic implications, younger children with higher respiratory rates are the ones who can benefit the most from an effective oral antibiotic alternative for the treatment of pneumonia.

1.5 Care seeking and access to care

ARI case management is a partnership between the health system and the family. Important elements of case management are care seeking, access to care, quality of care and follow-up. Appropriate care seeking includes early recognition of illness, assessment of the illness by the caretakers and seeking timely appropriate care.[67] Even if the caretakers recognize serious illness, they may not seek care.[68] Utilization of health facilities remains low in many parts of the world. In Bolivia[69] and Guinea[70] more than 60 per cent of children who died had not been taken to a formal health-care provider while ill. In Bangladesh,[71] only 8 per cent of sick children were first taken to appropriate health facilities. In Tanzania, only 41 per cent of sick children were taken to appropriate health facilities, and children of poorer families were less likely to receive antibiotics for pneumonia.[72] In children, a non-fatal disease can progress within a few days to a fatal outcome if appropriate care is not provided in time.[73-76] High mortality can result if the health facility is not easily accessible.[77,78] Even if parents/caretakers seek care, high case fatality can still result from delays in seeking care, inadequate triage and waiting times at health care facilities, failure to receive appropriate treatment, and drug and bed shortages.[79,80] Untreated infections lead to severe morbidity and high mortality.[67,69,76,79-80]

Prompt and effective treatment with antibiotics often involves bringing treatment closer to where the sick children are. Studies have demonstrated that trained community health workers (CHWs) are capable of managing pneumonia in the community.[73,85-89] The case management performed by

CHWs included classification of respiratory illness based on respiratory rates and lower chest indrawing, treatment of non-severe pneumonia with antibiotics, and, where possible, referral of severe pneumonia cases. A recent meta-analysis of community-based pneumonia case management studies estimated a 20% reduction in all-cause under-one mortality and a 24% reduction in all-cause under-five mortality.[90]

2. STUDY DESIGN

This study was *a one arm intervention study* which took place in 6 different countries including Egypt to assess the safety of treating severe pneumonia with oral amoxicillin for five days at home in children 3 to 59 months old.

2.1 Inclusion Criteria

Inclusion criteria for this study were as follows:

1. Children aged 3 to 59 months with severe pneumonia.

"Severe pneumonia was defined as lower chest indrawing in children with cough and/or difficult breathing, who were able to drink and did not have central cyanosis, regardless of the respiratory rate"

2. Informed consent by a legal guardian.

2.2 Exclusion Criteria

Children with any of the following conditions were excluded:

1. Very severe pneumonia/disease
2. Known prior episodes of asthma or three or more prior episodes of wheezing
3. Lower chest indrawing that resolves after three doses of bronchodilator therapy.
4. Severe malnutrition (visible severe wasting or edema)
5. Known anaphylactic reaction to penicillin or amoxicillin
6. Hospitalization in the last two weeks
7. Other diseases requiring antibiotic therapy at presentation, such as meningitis, dysentery, osteomyelitis, septic arthritis, evident tuberculosis, etc.
8. Persistent vomiting
9. Previous inclusion in the study or already included in another study
10. Living outside Ismailia governorate.
11. Parental or caretaker refusal to participate in the study
12. Study physician did not think that the family will comply with oral antibiotic therapy at home or the required follow-up visits, due to safety, risk of traveling to the hospital, etc.
13. Severe pneumonia with measles on presentation as these patients may have immune suppression.
14. Kerosene ingestion
15. Near drowning
16. Known or clinically recognizable chronic conditions (Down's syndrome, congenital

cardiac or respiratory anomalies, neurological impairment that affects respiratory function, chronic lung disease including bronchopulmonary dysplasia, renal diseases, malignant or hematological diseases).

2.3 Objectives

The overall goal was to evaluate whether it is safe to treat children aged 3 to 59 months with pneumonia and lower chest indrawing (LCI) (WHO-defined severe pneumonia) with oral amoxicillin.

2.3.1 Primary objective

To determine in children 3-59 months with pneumonia and lower chest indrawing:

- The proportion eligible for home therapy who fail treatment with oral amoxicillin by day 6

2.3.2 Secondary objectives

To determine in children 3-59 months with pneumonia and lower chest indrawing:

- The proportion eligible for home therapy who fail treatment with oral amoxicillin by day 14

- To identify baseline clinical predictors of treatment failure in children with severe pneumonia.

2.4 Outcome Variables

2.4.1 Primary Outcome

The primary outcome was treatment failure within the first 6 days for children as defined by:

1. Clinical deterioration occurring any time after enrollment.[1]
2. Inability to take oral medication due to persisting vomiting as assessed by study physician.[2]
3. Change or addition of antibiotics (see 3.5)
4. Hospitalization (in home managed patients) related to pneumonia or therapy with amoxicillin (relatedness determined by the DSMB).
5. Serious adverse event considered possibly or probably related to amoxicillin.
6. Actively declined further follow-up.
7. Loss to follow up on day 6.
8. Voluntary withdrawal of consent from study.

[1] Developing any sign of very severe disease such as central cyanosis, abnormally sleepy or difficult to wake, inability to drink, convulsions, or death

[2] Persisting vomiting defined as vomiting three repeated doses of oral amoxicillin within ½ hour of administration.

2.4.2 Secondary outcomes

The following secondary outcomes were assessed:

1. Treatment failure between day 6 and 14 (as defined in 'change of antibiotic' below).
2. Clinical deterioration (development of danger signs) between day 6 and 14.[1]
3. Development of lower chest indrawing or fast breathing which is non-responsive to three trials of nebulization with bronchodilator between day 6 and 14.[3]

2.5 Change of Antibiotic

Reasons for changing the antibiotic were:

1. Developing a co-morbid condition
2. Persistence of fever > 38^0C with lower chest indrawing on day 3 (after 72 hours).
3. Either fever or lower chest indrawing alone at day 6 or later

2.6 Enrollment of Subjects

2.6.1 Ethical Review

The study was submitted for review to the Institutional Review Board (IRB) of Suez Canal Faculty of Medicine, which accepted the study proposal to be conducted in Ismailia governorate.

2.6.2 Source of Subjects

Children who presented to the outpatient department of a participating centers with history of cough or difficult breathing and were found to have lower chest indrawing, according to the criteria mentioned above, were referred to a member of the investigation team. This individual performed the screening. If the child was eligible for outpatient home therapy, he was included in the study. The study was conducted in 7 primary health care centers in Ismailia governorate.

2.6.3 Screening

Children referred to the investigator were screened using Screening Form, to evaluate whether they fulfill each of the inclusion criteria and have none of the exclusion criteria. Children who are excluded from the study were treated according to standard procedures at the centers. Children who were included were screened for eligibility for home oral amoxicillin therapy. A parent or guardian of a child who fulfills the eligibility criteria was asked to provide consent for their child to participate in the study for oral amoxicillin therapy.

The child was assessed to determine whether he/she has severe pneumonia or not. We then asked if the caregiver is interested in participating in the study and if so, the screening and baseline

[3] Wheezing children will be given a trial of nebulised salbutamol (0.5ml plus 2.0 ml of sterile water or 2 puffs using a metered-dose inhaler with a spacer device) and re-evaluated after 15 minutes. If the LCI or fast breathing persists, a second trial of nebulisation will be given, failing which a third will be given.

assessment was completed. If the caregiver did not want the child to be enrolled in the study, the child was treated according to the standard protocol at each participating site. If the caregiver was interested in enrollment, the screening and baseline assessment was carried out expeditiously to begin antibiotic treatment for the child.

2.6.4 Procedures for Obtaining Informed Consent

The parents or legal guardians of the children eligible to enter the study were fully informed about the study in the Arabic language. The study physician obtained the freely given consent of the parents or legal guardian for the child to participate in the study. The content of the explanation provided to the parents or legal guardians of the children is described in the attached consent form. Parents had their questions fully answered and were given the time they need to consider the study before consenting.

2.6.5 Baseline Assessment

The baseline assessment was performed as quickly as possible after screening and provision of informed consent. The baseline assessment was carried out no more than 1 hour after presentation.

Data collected at baseline on the BASELINE FORM included:

- *Identification:* name, address, date and time of enrolment, gender, health unit record, parents' names, detailed description of location and other contact information, details of date of birth and/or age in months. All this information was recorded in the Identification form and was not included in the database.

- *History of present illness*, with particular emphasis on the use of breast-feeding, use of antibiotics, use of bronchodilators and immunization status.

- *Physical examination* included weight, length for < 24 months and height for > 24 months, axillary temperature, respiratory rate, lower chest indrawing*, state of the child during measurement of respiratory rate, presence of auscultatory wheezing, crackles (unilateral or bilateral), intercostal indrawing, suprasternal indrawing, bronchial breathing, diminished or absent breath sounds.

- *Assessment of lower chest indrawing*: Study physicians were trained how to assess lower chest indrawing. Some of the elements of this training are described below:
    - An initial training followed by practice on 10-20 patients were evaluated independently by the study physician and health workers, and revised by the field supervisors, were conducted at each health center.
    - A video developed by WHO/IMCI program that demonstrating fast breathing and lower chest indrawing in children was used as reference in the training of the physicians and health workers.
    - Study filed supervisors monitored and evaluated the study physicians' and community health workers' ability to assess lower chest indrawing.
    - Once every month the PI evaluated lower chest indrawing by study physicians or community health workers and reinforced training.

2.6.6 Urine Antibacterial Activity

Urine samples were obtained on all children upon entrance into the study to assess recent antibiotic usage. Specimens were centrifuged at 3000 g and the supernatant was sterilized by passage through a 0.22 μ filter (Swinnex). Samples were frozen at –20°C until assayed. At that time, samples were thawed and 10-20 μ were placed on a standard filter disc on a nutrient agar plate streaked with a lawn of a suitable pan-sensitive test organism (Section 3.6.7).[95] At least one disc was inoculated with pooled urine from children of the same age range as the study population who are known not to be taking antibiotics for two weeks (negative control) and another disk was inoculated with urine from a patient who was getting antibiotics for at least 8 hours as a positive control. Urine antibacterial activities were interpreted based on any zone of inhibition of the inoculated organism, around the disc, by 24 hours. Assessment of antibacterial activity in the urine of children enrolled in the study allowed sub-group analysis of treatment failure rates in children who received previous antibiotic therapy and in those without previous antibiotic therapy.

2.6.7 Microbiologic Assay of Urine for Presence of Antibiotic.

Presence of antibiotic in the urine was detected by testing urine specimens on the lawn of reference organism(s), which are sensitive to most of the antibiotics. More than one organisms was used to increase the sensitivity of the test and thus to detect all possible antibiotics in the urine.

The following organisms were used for this assay: *Micrococcus* letus ATCC-9341

Collection and processing of Urine Samples: The urine samples were collected following the aseptic procedure and centrifuged at 2500-3000 rpm for 5 minutes to sediment the debris etc.

Materials:

a) Mueller Hinton Agar.
b) Mueller Hinton Blood Agar.
c) Muller Hinton broth
d) Blank Disc.
e) Micropipettes to dispense 10μl

Methods: To perform this test, Mueller Hinton agar was used to detect the presence of antibiotic on Staphylococcus and E. coli strains, and Mueller Hinton agar with 5% sheep blood was used to carry out the test on Micrococcus strain.

Steps:

a) Grow/suspend the ATCC strains in Mueller Hinton Broth for 3-5 hours to match with 0.5 MacFarland standard.
b) Lawns were made on the dried agar plates, using a sterile cotton swab dipped in the broth and squeezed against the inner wall of the tube.
c) The plate dried for 5 to 10 minutes and the blank disks (6 per plate) placed on the plate.

d) The place of disks was labeled with ID of urine specimens, and impregnated it with 10µl of urine specimens accordingly.
e) The plates were incubated at 37^0C overnight and read for any zone of inhibition.

Interpretation: Any zone of inhibition against either of the organisms was considered as the indication for the presence of antibiotic in the urine.

2.7 Interventions

2.7.1 Observation period

Study patients were followed from the time of enrollment until 14 days after enrollment. Data were collected on standard data collection forms at the following times for all patients:

- At enrollment
- On day 1 (24 hours after enrollment)
- On day 2
- On day 3
- On day 6
- On day 14

If the patient was well on the fourteenth day, the patient was deemed cured and no further follow-up occurred.

If the patient was unwell on the fourteenth day, as determined by the study physician, the patient was managed as per standard hospital practice.

FINAL OUTCOME FORM was completed on Day 14.

2.7.2 High Dose Amoxicillin Administration

Amoxicillin was provided to the mother as a suspension. A total of 80-90mg/kg per day for 5 days was given to the children; that is to say 40-50mg/kg per dose in 12 hourly oral dose. Mothers were instructed to give a second does when the child vomits within half an hour of the initial dose of amoxicillin. The mother was instructed to repeat this for a total of three attempts. Based on an oral suspension concentration of 250mg/5mL, dosing was adjusted as follows:

Table II Dose of oral amoxicillin (250mg/5mL)

Weight	**12 hourly oral dose**
3 – 5 kg	5.0 mL (1 medicine spoon)
6 – 9 kg	7.5 mL (1 ½ medicine spoon)
10 – 14 kg	12.5 mL (2 ½ medicine spoon)
15 – 19 kg	17.5 mL (3 ½ medicine spoon)

2.7.3 Ambulatory Management

After assessing eligibility for enrollment in the study, the mother/caretaker was shown how to give the amoxicillin dose. The first dose was administered by the mother/caretaker under supervision in the health facility. No other antibiotics were allowed while the child was enrolled in the study. Study patients who require additional antibiotics subsequent to enrollment, *were declared treatment failures,* but follow-up of these patients continued until resolution of the morbid episode.

2.7.4 Clinical Assessment

Data were collected on standard data collection forms. Evaluation either at health facility or home included the following:

Table III

Evaluation	**Description**
Temperature	Axillary
Respiratory rate	Measured over 60 seconds – child not crying
Lower chest indrawing	Training as described previously
Pulse rate	Palpation over 60 seconds
Staff monitoring for clinical deterioration	Inability to drink Stridor in a calm child Cyanosis, and convulsions Grunting
Other signs which staff felt relevant (e.g., co-morbid conditions).	

2.7.5 General Supportive Care in the Ambulatory Setting

- *Bronchodilators:* Children were given oral bronchodilators (salbutamol syrup 0.15mg/kg/dose) if clinically suspected to have a wheeze on any clinical assessment.
- *Fever:* Patients with axillary temperature (actual reading) equal or greater than 38^{o}C, as measured by a thermometer received oral paracetamol in the dose of 10-15 mg/kg/dose as needed, with a minimum period of 6 hours between doses. Mothers were advised to administer paracetamol if they suspect fever in their child.
- *Feeding:* Nursing mothers were encouraged to continue breast feeding. Children received normal diet during the illness.
- *Hydration:* If present was managed according to standard WHO rehydration protocol.
- *Nasal secretions:* Patients with significant nasal secretions had the nose cleared by gentle suction and nose drops (saline) instilled if necessary, according to the standard practice.
- *Anti-histamines and cough syrups* were not used in any of the children as they have no beneficial effect, make children drowsy and interfere with the accuracy of the other assessments.
- *Other medications* such as anti-convulsants for children with a history of a seizure disorder was allowed and recorded on the case report forms.

2.7.6 Information to Mothers for Home Management

The mother/caregiver of patients who were eligible to receive home treatment with oral amoxicillin was counseled to continue with the oral treatment prescribed for a period of 5 days. They were advised to return to the healthcare facility at any time during the study period and for two weeks thereafter, if symptoms recurred or if the child developed danger signs. These symptoms were clearly discussed with the mother as described in the "patient discharge counseling checklist". Mothers were given a "study patient data card" identifying the child as a study patient, and listing the telephone numbers where study staff can be contacted.

2.8 Follow-Up and Outcome Assessment

2.8.1 Ambulatory Management Follow-up:

The patients were sent home to complete 5 days of oral therapy. They were monitored for a total of 14 days. They were evaluated at the following times:

Table IV Follow-up assessment

Day of data collection	Site of assessment
At enrollment (Day 0)	Health facility
Day 1 (after 24 hours)	Home
Day 2	Home
Day 3	Home
Day 6	Home
Day 14	Health facility

The caregivers were reimbursed for transportation cost to the health facility. If the patient did not return to the health facility on day 14, they were visited at home within the next 24 hours. If the patient was well on the fourteenth day, the patient was deemed cured and no further follow-up was done. If the patient was unwell on the fourteenth day, as determined by the study physician, the patient was managed as per standard practice.

2.8.2 Home Follow-up

Children were followed up at home on Day 1, Day 2, Day 3 and Day 6. Children who did not appear for their clinic appointment on Day 14 were actively traced for evaluation at home. The reason for default was ascertained at the end of their "due-day". If the reason for default was other than death, voluntary withdrawal from the study or a move out of the study area, the investigator attempted to see the child the next day. Children who could not be traced at home were declared "lost to follow-up", and a FINAL OUTCOME form was completed. Similarly, the child was declared "lost to follow-up" if default was due to a move out of the study area or withdrawal. If the child had died since enrollment in the study, the visit form for that day (i.e. Day 14) was completed as appropriate.

2.8.3 Unscheduled Follow-up

Patients, who were brought back to the health center or to the university hospital by their care-giver at times other than the designated follow-up visits, were clinically assessed by the study physicians

and decisions were made regarding their further management. This information was recorded on the follow-up CRF and treatment failure form.

2.8.4 Discontinued Patients

Study physicians followed children who were discontinued from the study for 14 days from enrollment or until such time as they were well, and they ensured that they had appropriate treatment and follow-up arrangements. Children who were discontinued from the study because of voluntary withdrawal by the parent/guardian, or removed from the hospital against medical advice, were not followed by the study physicians. If there was concern about the well being of a study patient who was removed from hospital against medical advice, the relevant social services at the site was informed.

2.8.5 Referral to Health Facility by Health Workers

Community health extenders (i.e. nurses and other non-doctor health care workers) clinically evaluated children at home on days 1, 2, 3, and 6 of the study. For any child in whom there was concern for treatment failure, community health extenders were instructed to refer the child to the health facility for evaluation by the study physician. The study physician assessed the child and determined if the child meets criteria for treatment failure. If so, the child was managed and treated per the study physician's clinical judgment and the usual practices of the participating health center.

2.8.6 Treatment Failure and Therapy Change for Ambulatory and Hospitalized Patients

Any time the study physician suspected a treatment failure, he or she contacted the Site Coordinator to confirm the treatment failure. At this time antibiotic therapy was changed and other appropriate therapy was started. All cases of treatment failure were followed up until considered well.

2.8.7 Withdrawals from the Study

A child was discontinued from the study if there was treatment failure or parent or guardian withdraws their consent, which was documented on the appropriate form.

2.8.8 Clinical Care of Children Who were Discontinued from the Study

Children classified, as treatment failures received antibiotic therapy as directed by their physician. If the child was hospitalized, the physician obtained additional chest radiographs, blood counts and other laboratory tests to aid patient management according to clinical judgment and the usual practices of the hospital.

Children who experience serious adverse events discontinued the study therapy. Antibiotics other than penicillin related drugs were given to these patients, as well as bronchodilators, paracetamol, and other therapy as appropriate.

Parents who refused to have their child continue to participate in the trial at any time were advised about general care of the child and how to recognize increasing severity of illness. These children were treated according to their clinical condition by the time of withdrawal.

2.8.9 Assessment of Adherence

Adherence was evaluated at each follow-up visit by asking mothers how the antimicrobial agent had been administered and by checking the marked cells on the bottle label. The amount of drug remaining in the bottles was assessed by the visiting health worker. Patients were considered compliant if the caregiver reported administering the medicine as instructed, and if the child had taken 80% of the medicine in the bottle by day 6.

2.9 ADVERSE EVENTS

The Site Coordinator carefully monitored each child for adverse events. If an adverse event occurred, the investigator assessed its duration, seriousness, intensity and relationship to the administration of the study medication (amoxicillin). The site coordinator used their judgment about whether to continue the child in the study or to discontinue enrollment. The event and its treatment was reported on appropriate form and immediately reported to the local study PI.

2.8.10 Definitions of Adverse Events

- *Adverse event* - any undesired experience occurring in a child during a study, whether or not the event is considered to be related to the therapy under investigation.

- *Serious adverse event* - any fatal, life-threatening, disabling event or event that results in hospitalization or prolongation of hospitalization. Congenital anomaly and malignancy are always considered serious adverse events.

- *Unexpected adverse event* - an experience not previously reported (nature, severity or incidence) in the currently provided drug data sheets or package inserts.

All serious AEs, including those observed by study personnel or problems, complaints, signs or symptoms volunteered by the child or their parent or guardian and diagnoses were recorded on the serious adverse event case report forms provided, regardless of whether they were believed to be associated with the study treatment. If a definitive diagnosis of the adverse events was not possible, individual signs and symptoms were reported.

2.8.11 Relationship to the Study Drug

The relationship of the study drug to an adverse event was classified as none, remote, possible, probable or not assessable. The decision was clinical, based on all available information at the time of completion of the forms. Factors considered included:

- Temporal relationship between drug administration and occurrence of the event. The event if occurred after the drug was administered, it is considered related to drug administration. The length of time from drug exposure to event was evaluated in the

clinical context of the event.

- Recovery on discontinuation (dechallenge), or recurrence on re-introduction (re-challenge).
- Underlying, concomitant, intercurrent illness. The event was evaluated in the context of the natural history of the disease being treated and any other diseases that the patient had.
- Concomitant medication or treatment. Other medications that the patient was taking, was examined to determine whether any were known to cause the event in question.
- Known response pattern for this class of drug.
- Exposure to physical or mental stresses. Any exposure to stress that might caused changes in the recipient and provided a logical better explanation for the event.

2.8.12 Severity of an Adverse Event

The intensity (severity) of the event was classified as:

- Mild - transient, not interfering with the child's activities;
- Moderate - causes sufficient discomfort to interfere with the child's activities;
- Severe - incapacitating and prevents normal activities.

If the intensity changed over time, the maximum intensity was recorded.

2.8.13 Risks and Discomforts

Diarrhea or skin rash that developed due to antibiotic use were recorded. Clinical deterioration at home was a risk factor that was reported in the consent forms.

3. STATISTICAL CONSIDERATIONS

3.1 Sample Size

This was a prospective multi-center one-arm intervention study. All children were evaluated to determine whether they were eligible for home management for treatment of severe pneumonia with oral amoxicillin. The study determined the proportion of treatment failures in children receiving oral amoxicillin. All children received standard supportive care.

3.1.1 Criteria used to estimate sample size

To determine the sample size, the current assumptions were used:

- **Anticipated Failure** –14% or fewer of children treated with oral amoxicillin at home will fail treatment as defined in section 2.4.1, at or before 6 days of observation

  Justification - The proportion of treatment failures is estimated at 14%, based on the results of APPIS. Although APPIS reported a 19% treatment failure with oral amoxicillin at 48 hours, the failure rate in this study is anticipated to be lower as 8% of children in APPIS who had lower chest wall in-drawing alone on study day 2 were declared treatment failure,

but will not be declared treatment failures at this time point in the current study. This treatment failure rate of 14% includes a loss to follow-up of 3% or less.

- **95% confidence interval of ± 5%**

  Justification - Based on a consensus of the site principal investigators, we have focused on determining the sample size needed to assess the upper limit of the two sided 95% confidence interval is no greater than 19% (i.e. ± 5%). No adjustments have been made for multiple comparisons because there is only one primary hypothesis.

- **Loss to follow-up 3% or less**

  Justification – This study will require outpatient follow-up in large urban areas. If follow-up is carefully and diligently performed, it will be possible to keep loss to follow-up at 3% or less. The estimated proportion of loss to follow-up has been based on previous data from the APPIS study as well as data from several previous ARI studies conducted in Pakistan. In the APPIS study, cumulative loss to follow-up was 3.1% and this study included follow-up at two and five days as an inpatient followed by a two-week outpatient follow-up. Based on this data, it was felt that a 3% loss to follow-up was achievable for the purposes of this trial.

3.1.2 Sample Size Estimate

Sample size estimates are based on standard formulae for calculating a two-sided 95% confidence interval for a single proportion using the large sample normal approximation.[96] The required number of patients is given by the following formula:

$$N = \left(Z^2_{\alpha/2}(pq)\right)/d^2$$

where N= sample size, p is the observed proportion, q=1-p, $z_{\alpha/2}$=1.96 and d is the width of one side of the 95% confidence interval. Using the assumptions listed above, the required number of children to be enrolled in this observational study for evaluation of the primary endpoint was **186**.

Based on APPIS screening data, we estimated that about 30% of children with severe pneumonia will not be eligible for oral therapy, mostly because of previous or concurrent co-morbid conditions; therefore we estimate that approximately 70% of children with severe pneumonia will be eligible for outpatient therapy with oral amoxicillin.

3.1.3 Power for Studying Secondary Endpoints

Cumulative treatment failure at 14 days is estimated to be 16% based on results of APPIS. This includes an estimated 2% who will receive other antibiotics and/or develop comorbid conditions and an estimated additional 3% who will be lost to follow-up and this generates a sample size of **207** study patients for evaluation of the secondary endpoint. With 207 study patients, in whom we anticipate a treatment failure rate of 16% at day 14, we will have sufficient sample size to report a two-sided 95% confidence interval for the expected proportion of 16% ± 5% (using the above formula).

3.1.4 Sample Size in Suez Canal University site:

The study team in the Suez Canal University Egypt site recruited 237 children, which was enough sample size to achieve both the primary and secondary study objectives and endpoints.

3.2 Statistical Analyses

3.2.1 Preparation of the Analysis Data Set

All case report forms audited, against the medical record, on site before the data were entered locally or a copy of the case report form was forwarded for data entry. The data audit included visual screening for missing data and inconsistencies. All out of range values, inconsistencies and missing data were sent to the site for resolution. Preplanned construction of new variables was conducted in accordance with the study hypotheses and analysis plans. Data reduction involved selection of the most important variables to be included in the final analyses. Since some variables may appear to duplicate others, selection of the final study variables depends on measurement reliability, precision and extent of missing data. A conservative approach was taken for missing data for treatment failure on day 6 and 14, when children who were lost to follow-up were assumed to have failed treatment.

3.2.2 Final Analyses

All study variables were summarized using descriptive statistics – mean and standard deviation for normally distributed variables, median and interquartile range for continuous, non-normally distributed data and proportions for categorical data.

- *Primary end-point* - We reported the proportion of children who failed home management with oral amoxicillin on or by day 6, with the 95% confidence interval.

- *Secondary end-points* - We reported the proportion of children who failed home management with oral amoxicillin between day 6 and day 14 with the 95% confidence interval.

4. DATA MANAGEMENT

4.1 Data Collection

The study coordinator completed all appropriate case report forms up to the time that the child is discontinued from the study. Study data were collected on Case Report Forms (CRF). Each month, the site PI or his/her designate visually edited the CRF for each child who had completed or withdrawn from the study. All missing data were identified and every attempt was made to complete missing data.

4.2 Management of Study Materials at Clinical Sites

The study team kept track of all patients screened and enrolled and a also kept a filing system of all study related records - case history records, study protocol or related documentation and drug distribution records

4.3 Case History Records

These included the study case report forms that contained information that documents the child's eligibility to participate in the study, the signed consent form, and information from tests and examinations. Copies of supporting documentation for the information contained in the CRF were kept with each patient's case history record. This supporting documentation included records of physical examinations, progress notes, laboratory reports, X-rays, consultations, correspondence, information and data on the subject's condition, during and after the clinical investigation, diagnoses made, concomitant therapy, etc. Each child's case history record was evaluated to verify validity and completeness of the data.

4.4 Study Protocol and Related Documentation

All study related documents including the study protocol, manuals of operations, all correspondence sent to or received from the study monitor, materials used for obtaining informed consent, protocol modifications and records of the Institutional Review Board approval and all communications with the IRB must be maintained in complete form at each site. These documents were evaluated to ensure that study documentation was complete.

4.5 Record Retention

All records were retained and electronic data were de-identified, unlinked from any personal identifiers to protect individual identity.

4.6 Monthly reports

Monthly reports of enrollments and exclusions were reported monthly to the INCLEN Central Offices, both in New-Delhi and Philadelphia.

4.7 Reporting of Serious Adverse Events, Treatment Failures and Deaths

Amoxicillin is in widespread use and is not investigational in the study site. However, since oral amoxicillin is not recommended for initial treatment of children who have severe pneumonia, the appropriate case report forms describing the occurrence of a serious adverse event, treatment failure or death were reported immediately to the study PI. The PI sent a copy of the adverse event data to the local IRB.

4.8 Compliance with and Deviations from the Study Protocol

The Site coordinator was responsible for making sure that the protocol was strictly followed. There were no deviations from the original study protocol.

4.9 Data Entry

The study team entered the data at the site and it will be provided to the coordinating center. All data forms were entered into the data entry files and cleaned on site...

4.10 Transfer of Case Report Forms to the IRCC

Suez Canal study team did not use auto-copying forms, and a photocopy of the original data collection forms are available for review or auditing by the coordinating center

4.11 Back up and Security

To avoid possible confusion about the most recent version of data files, the internal clock on the computer used for data entry were set with the correct date and time.

4.12 IRCC Reports

Regular reports were sent to the coordinating center monthly, which included both technical and financial reports.

5. FORMS

5.1 Consent Form

This form was prepared and translated into the local Arabic language. Every patient's caretaker was told about the included information and asked if he agrees to participate in the study. If he agreed, the child was included in the study. Caretakers who refused to participate in the study were treated according to the routine management in the health center.

5.2 Identification Form

This form was filled out for all **enrolled** participants and kept in the front of the study record. It was used primarily as a source of information for participant contact. This form contains participant identifying information. The accurate address for each subject was written carefully. If a street address is not available, then a map was drawn, as the ability to find the home where the child was located was critical to the follow-up evaluations which were done at the child's home on Day 1, Day 2, Day 3 and Day 6.

5.3 Screening Form

The screening form contains the inclusion and exclusion criteria for the study. This form was filled out for each individual who was assessed for enrollment in the study. This form was completed for all **assessed** individuals. If any exclusion criteria were present the child was not enrolled in the study.

5.4 Baseline Form

The baseline form was completed immediately after enrollment.

5.5 First Follow-up Form (Day 1)

This form was completed at the time of the First Follow-up Visit. Comments about acceptance, reactions or other relevant clinical observations were record.

5.6 Second Follow-up Form (Day 2)

This form was completed at the time of the Second Follow-up Visit.

5.7 Third Follow-up Form (Day 3)

This form was completed at the time of the Third Follow-up Visit.

5.8 Fourth Follow-up Form (Day 6)

This form was completed at the time of the Fourth Follow-up Visit.

5.9 Fifth Follow-up Form (Day 14)

This form was completed at the time of the Fifth Follow-up Visit.

5.10 Final Outcome Form

This form contained results of the laboratory investigations.

5.11 Laboratory Reporting Form

This form was for reporting the results of the urine antimicrobial testing done on the sample obtained at enrollment.

5.12 Adverse Events Form

Adverse events and treatment failure were reported for children regardless of the treatment that they had received (oral Amoxycillin) to allow appropriate interpretation of this critical information.

5.13 Patient Discharge Counseling Checklist

5.14 Patient Card

6. Study Area and Study Population

The study was conducted in Ismailia Governorate, which has a population of 800,000, nearly equally divided between urban and rural communities. The governorate lies in the middle of the Suez Canal Zone, along the west bank of the canal. Ismailia city is the capital of Ismailia Governorate. It is situated 100 Km. to the east of Cairo city, and has a population of about 300,000. (See the maps of Ismailia Governorate)

Ismailia governorate has an efficient and well-structured health system. It has 62 different health facilities, which offer health services to over 150,000 persons every year. In the urban area there are 38 health facilities, while in the rural area there are 24 health facilities (CAPMAS, 1997).

The study was conducted in seven rural primary health care centers in Ismailia governorate. It included 237 children aged 3-59 months of age, with mean age of 12.42 $\pm$ 10.05 months, presenting to the outpatient clinic of the participating centers with signs of severe pneumonia.

7. Study Results

Clinical cure rate with 5 days amoxicillin therapy at day 6 was 90.7% (primary outcome) [fig-1], while clinical cure rate at day 14 was 87.4% (secondary outcome) [Table-1. Failure of therapy at day 6 occurred more frequently in patients of low weight [p= 0.01] and in those with rapid respiratory rate (>50/minute), while no other studied demographic and clinical characteristics were statistically significant [Tables 1,2, & 3].

Three patients (1.3%) were lost to follow up, 3 patients were hospitalized (1.3%) and there were no deaths. Patients lost to follow-up and hospitalized patients were considered treatment failures. Adverse effects occurred in 14 treated children (5.9%) in the form of mild diarrhea, and combined vomiting and diarrhea in one patient. Urine examination for antibiotics use before Amoxicillin treatment showed that 15 out of 155 children (9.7%) received antibiotics; however, there were no difference between cured or failed treated patients on antibiotics use before therapy [Table-4].

Study Strengths and Limitations

The main strengths of the study were that it was large, ambulatory management, community-based, and was conducted over one year with minimal loss to follow-up. Its limitations are that follow-up was limited to 14 days, children with asthma were excluded and causes of infection were not investigated.

Conclusion

- Oral amoxicillin is effective and safe in treating pneumonia in children in ambulatory setting, when given for 5 days in a dose of 80-90 mg/kg/day in 2 divided doses.
- Minor adverse effects occurred in small proportion of treated patients and did not affect cure rate.
- Failure of therapy occurred more frequently in patients of low weight and in those with rapid respiratory rate (>50/minute).

Significance

Five day course of amoxicillin for treating children with non-severe pneumonia in ambulatory setting was effective and safe in this community-based study. These findings if proved to be compatible with findings presented in the other centers of the multicenter study could have global implications for a cost-effective management of childhood pneumonia.

Table 1: Number of failure cases in the different follow-up days

Clinical Assessment	Number
- Failure at day 1	3
- Failure at day 2	8
- Failure at day 3	6
- Failure at day 6	5
Total failure at day 6 (Primary Outcome)	22
Relapse at day 14 (Secondary Outcome)	8

Table 2: Comparison of Demographic and Clinical baseline characteristics of cured vs. failed treated patients at day 6

Characteristics & Clinical Findings	**Cured at day 6 (N=215)**	**Failure at day 6 (N=22)**	**t-test**	**P-value**	**All Data (237)**
- Age (Mean $\pm$ SD)	12.81 ± 10.45	13.73 ± 6.34	0.60	0.551	12.42 ± 10.05
- Weight [kg] (Mean $\pm$ SD) -	9.47 ± 4.86	7.86 ± 2.33	2.70	0.010*	9.32 ± 4.698
- Height [cm] (Mean $\pm$ SD)	71.26 ± 10.91	67.88 ± 9.07	1.40	0.162	70.94 ± 10.79
- Temp. [C^o] (Mean $\pm$ SD)	37.56 ± 1.34	37.66 ± 0.51	0.70	0.484	37.57 ± 1.29
- R.R. / min (Mean $\pm$ SD)	49.62 ± 9.99	58.98 ± 8.74	4.23	0.000*	50.5 ± 10.69

*** Statistically Significant (t-Test).**

Table 3: Comparison of Demographic and Clinical Baseline Characteristics of Cured vs. failed Treated Patients at Day 6

Characteristics & Clinical Findings	Cured at Day 6	Failure at Day 6
- Sex (Males/Total)	59.1%	59.1%
- Fever	74.9%	63.3%
- Cough	96.7%	95.5%
- Difficult breathing	62.3%	63.6%
- Vomiting	15.3%	13.6%
- Diarrhea	5.6%	9.1%

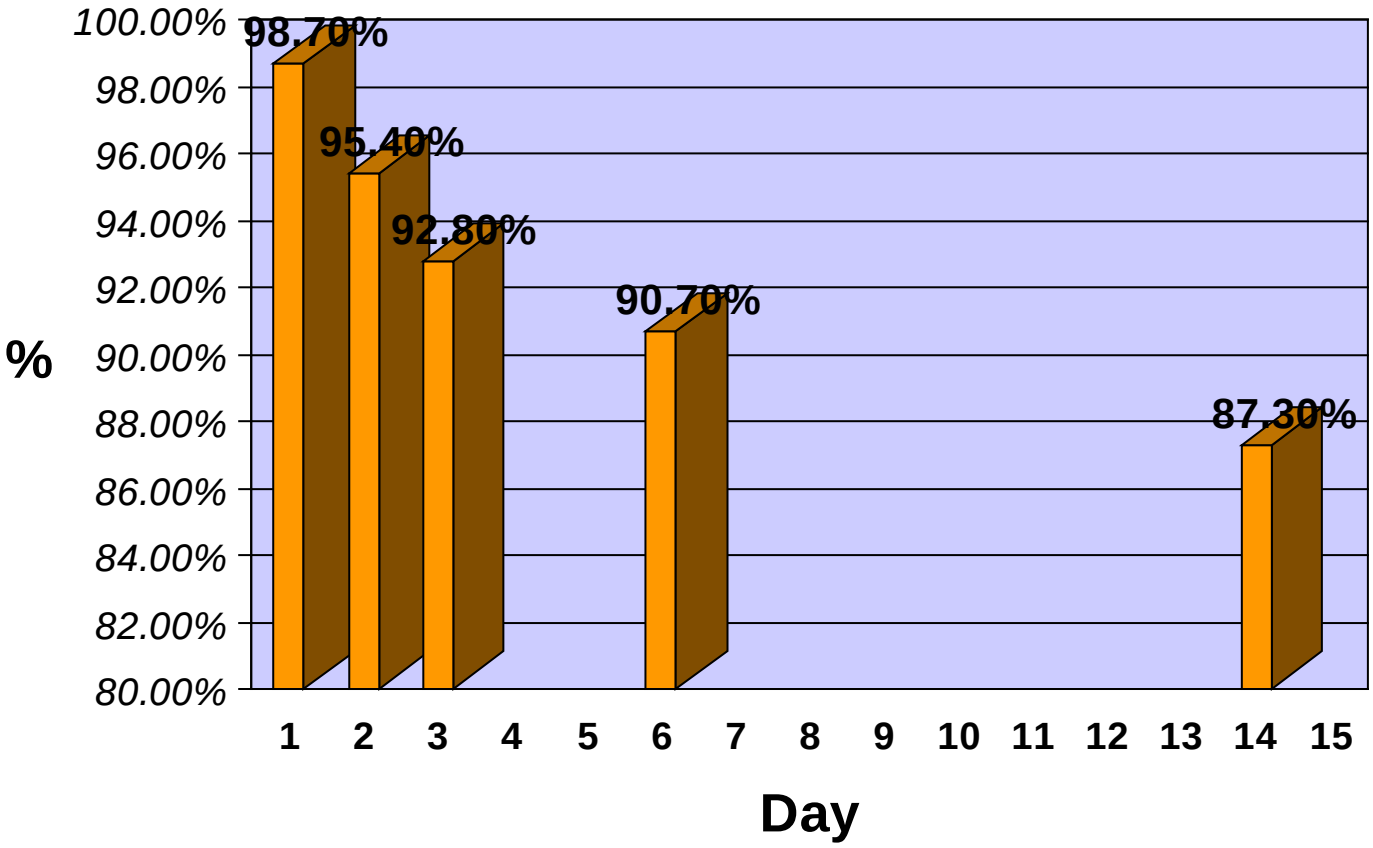
No statistical difference between the two groups

Table 4: Comparison of cured and failed treated patients that received antibiotics before receiving amoxicillin therapy.

	Received Antibiotics	No Antibiotics Received
Success	14	128
Failure	1	12
Total	15	140

P value (Fisher Exact) = 1.000

Fig 1: Cure Rate of Treated Patients



REFERENCES

1. Williams BG, Gouws E, Boschi-Pinto C, Bryc J, Dye C. Estimates of worldwide distribution of child deaths from acute respiratory infections. Lancet Infections Diseases 2002; 2:25-32.
2. World Health Organization. Mathers CD, Murray CJL, Lopez AD and Stein C. The global burden of disease 2000 project: objectives, methods, data sources and preliminary results. Evidence and information for Policy (EIP). Geneva: World Health Organization 2001, URL: http://www3.who.int/whosis/discussion_papers/discussion
3. Qazi SA, Rehman GN, Khan MA. Standard ARI case management on antibiotic use and case fatality on ARI patients at a Children's Hospital in Pakistan. Bulletin of World Health Organization 1996;74:501-507.
4. Singhi S, Jain V, Gupta G. Paediatric emergencies at a tertiary care hospital in India. J Trop Pediatr 2003;40:207-11.
5. Pepin J, Demers AM, Mberyo-Yaah F, Jaffar S, Blais C, Somse P et al. Acute lower respiratory infections among children hospitalized in Bangui, Central African Republic: toward a new case-management algorithm. Trans R Soc Trop Med Hyg 2001;95:410-7.
6. WHO Programme for the Control of Acute Respiratory Infections. Technical basis for the WHO recommendations on the management of pneumonia in children at first level health facilities. WHO/ARI/91.20. Geneva : World Health Organization, 1991.
7. Vuori-Holopainen E, Peltola H.Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. Clin Infect Dis. 2001;32:715-26.
8. McIntosh K. Community-acquired pneumonia in children. N Engl J Med. 2002 Feb 7;346(6):429-37.
9. Ruuskanen O, Mertsola J. Childhood community-acquired pneumonia. Semin Respir Infect. 1999;14:163-72.
10. Korppi M, Heiskanen-Kosma T, Kleemola M. Incidence of community-acquired pneumonia in children caused by *Mycoplasma pneumoniae*: serological results of a prospective, population-based study in primary health care. Respirology. 2004;9:109-14.
11. Heiskanen-Kosma T, Korppi M, Laurila A, Jokinen C, Kleemola M, Saikku P *Chlamydia pneumoniae* is an important cause of community-acquired pneumonia in school-aged children: serological results of a prospective, population-based study. Scand J Infect Dis 1999;31:255-9.
12. Principi N, Esposito S. Emerging role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in paediatric respiratory-tract infections. : Lancet Infect Dis. 2001;1:334-44.
13. Gendrel D, Raymond J, Moulin F, Iniguez JL, Ravilly S, Habib F, Lebon P, Kalifa G.. Etiology and response to antibiotic therapy of community-acquired pneumonia in French children. Eur J Clin Microbiol Infect Dis 1997 May;16(5):388-91
14. Rastawicki W; Kaluzewski S; Jagielski M Occurrence of serologically verified Mycoplasma pneumoniae infections in Poland in 1970-1995. Eur J Epidemiol 1998 Jan;14(1):37-40
15. Forgie IM, O'Neill KP, Lloyd-Evans N et al. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital. Pediatr Infect Dis J. 1991; 10:33-41.
16. Ghafoor A, Nomani NK, Ishaq Z et al. Diagnoses of acute lower respiratory tract infection in children in Rawalpindi and Islamabad, Pakistan. Rev Infect Dis 1990; 12 (Suppl 8): S907 – S914.
17. Hietala J, Uhari M, Tuokko H, Leinonen M. Mixed bacterial and viral infections are common in children. Pediatr Infect Dis J. 1989 Oct;8(10):683-6.
18. Juven T, Mertsola J, Waris M, Leinonen M, Meurman O, Roivainen M, Eskola J, Saikku P, Ruuskanen O. Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J. 2000 Apr;19(4):293-8.
19. Korppi M, Leinonen M, Koskela M, Makela PH, Launiala K Bacterial coinfection in children hospitalized with respiratory syncytial virus infections. Pediatr Infect Dis J. 1989 Oct;8(10):687-92.
20. Tupasi TE, Lucero MG, Magdangal DM et al. Etiology of acute lower respiratory tract infection in children from Alabang, Metro Manila. Rev Infect Dis 1990;12(Suppl 8):S929-39.
21. Madhi SA, Klugman KP; Vaccine Trialist Group. A role for Streptococcus pneumoniae in virus-associated pneumonia. Nat Med. 2004 Aug;10(8):811-3
22. WHO Programme for the Control of Acute Respiratory Infections. Acute respiratory infections in children : case management in small hospitals in developing countries. WHO/ARI/90.5. Geneva : World Health Organization, 1990.

23. World Health Organization. Antibiotics in the treatment of acute respiratory infections inn young children. Programme for the control of acute respiratory infections. World Health Organization, Geneva. WHO/ARI/90.10.
24. Al-Eidan FA, McElnay JC, Scott MG, Kearney MP, Troughton KE, Jenkins J. Sequential antimicrobial therapy: treatment of severe lower respiratory tract infections in children. J Antimicrob Chemotherapy. 1999;44:709-15.
25. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. Bull World Health Organ. 1999;77(10):789-800.
26. Peterson S, Nsungwa-Sabiiti J, Were W, Nsabagasani X, Magumba G, Nambooze J et al. Copingwith paediatric referral--Ugandan parents' experience. Lancet 2004; 363(9425):1955-1956.
27. Jarvis WR.Controlling healthcare-associated infections: the role of infection control and antimicrobial use practices. Semin Pediatr Infect Dis. 2004 Jan;15(1):30-40.
28. Pong A, Bradley JS. Clinical challenges of nosocomial infections caused by antibiotic-resistant pathogens in pediatrics. Semin Pediatr Infect Dis. 2004 Jan;15(1):21-9. Review.
29. Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B, and the Pakistan Cotrimoxazole Study Group. Antimicrobial resistance and clinical effectiveness of cotrimoxazole versus amoxycillin for pneumonia among children in Pakistan: randomized clinical trial. The Lancet, 1998;352:270274.
30. Addo-Yobo E, Chisaka N, Hassan , Hibberd , Lozano J, Jeena P, MacLeod WB, Maulen I, Patel A, Qazi S, Thea D and Nguyen NTV and APPIS study group. A randomized multicentre equivalency study of oral amoxicillin versus injectable penicillin in children aged 3 to 59 months with severe pneumonia. Lancet 2004;364:1141-48.
31. UNAIDS. 2004 Report on the global AIDS epidemic. UNAIDS 2004. Geneva, 2003. 04.16E. http://www.unaids.org/bangkok2004/GAR2004_pdf/UNAIDSGlobalReport2004_en.pdf (accessed on 11.8.04)
32. World Health Organization. Report of a consultative meeting of children with pneumonia and HIV infection Harare 30-31 January 2003. WHO Geneva 2004.
33. Petri WA Jr. Antimicrobial Agents: Penicillins, cephalosporins and other Beta lactum antibiotics. In Hardman JG and Limbird LE (eds), Goodman and Gilman's the pharmacological basis of therapeutics, 10th Ed McGraw Hill New York 2001: 1189-1206.
34. Jadavji T, Law B, Lebel MH, Kennedy WA, Gold R, Wang EE. A practical guide for the diagnosis and treatment of pediatric pneumonia. CMAJ. 1997;156:S703-11.
35. British Thoracic Society. Guidelines for the management of community acquired pneumonia in children. Thorax 2002;57:i1-i24
36. Klugman KP. Pneumococcal resistance to antibiotics. Clin Microbiol Rev. 1990 Apr;3(2):171-96.
37. Klugman KP.Bacteriological evidence of antibiotic failure in pneumococcal lower respiratory tract infections. Eur Respir J Suppl. 2002 Jul;36:3s-8s.
38. World Health Organization. WHO Global Strategy for containment of antimicrobial resistance. WHO Geneva 2001. WHO/CDS/CSR/DRS/2001.2.
39. Kristinsson KG. Epidemiology of penicillin resistant pneumococci in Iceland. Microb Drug Resist 1995;1:121-125
40. Baquero F, Garcia-Rodriguez JA, Garcia de Lomas J, Aguilar LAntimicrobial resistance of 1,113 Streptococcus pneumoniae isolates from patients with respiratory tract infections in Spain: results of a 1-year (1996-1997) multicenter surveillance study. The Spanish Surveillance Group for Respiratory Pathogens. Antimicrob Agents Chemotherapy. 1999 Feb;43(2):357-9.
41. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S,Gudmundsson S Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. BMJ. 1996 Aug 17;313(7054):387-91.
42. Arnold KE, Leggiadro RJ, Breiman RF, Lipman HB, Schwartz B, Appleton MA, Cleveland KO, Szeto HC, Hill BC, Tenover FC, Elliott JA, Facklam RR. Risk factors for carriage of drug-resistant Streptococcus pneumoniae among children in Memphis, Tennessee. J Pediatr. 1996 Jun;128(6):757-64.
43. Yagupsky P, Porat N, Fraser D, Prajgrod F, Merires M, McGee L, Klugman KP, Dagan R. Acquisition, carriage, and transmission of pneumococci with decreased antibiotic susceptibility in young children attending a day care facility in southern Israel. J Infect Dis. 1998 Apr;177(4):1003-12.
44. Pallares R, Gudiol F, Linares J, Ariza J, Rufi G, Murgui L, Dorca J, Viladrich PF. Risk factors and response to antibiotic therapy in adults with bacteraemic pneumonia caused by penicillin-resistant pneumococci. N Engl J Med. 1987 Jul 2;317(1):18-22.

45. Amitai Y, Rotenberg M, Wirtschafter D, Haas H, Michel J. ncreasing frequency of penicillin-resistant pneumococci: epidemiological aspects and case-control study. Isr J Med Sci. 1985 Apr;21(4):340-5.
46. Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroedan F,Bouvenot G, Eschwege E.Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. JAMA. 1998 Feb 4;279(5):365-70.
47. Hoberman A, Paradise JL, Cohen R. uration of therapy for acute otitis media. Pediatr Infect Dis J. 2000 May;19(5):471-3.
48. Cohen R, Levy C, Boucherat M, Langue J, Autret E, Gehanno P, de La Rocque F.Five vs. ten days of antibiotic therapy for acute otitis media in young children. Pediatr Infect Dis J. 2000 May;19(5):458-63.
49. Low DE, Scheld WM.Strategies for stemming the tide of antimicrobial resistance.JAMA. 1998 Feb 4;279(5):394-5.
50. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. Microb Drug Resist. 1997 Summer;3(2):117-23.
51. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, Huovinen P. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med. 1997 Aug 14;337(7):441-6.
52. Vuori-Holopainen E, Peltola H, Kallio MJ; SE-TU Study Group. Narrow- versus broad-spectrum parenteral anatimicrobials against common infections of childhood: a prospective and randomized comparison between penicillin and cefuroxime. Eur J Pediatr. 2000;159:878-84.
53. Peltola H, Vuori-Holopainen E, Kallio MJ; SE-TU Study Group. Successful shortening from seven to four days of parenteral beta-lactam treatment for common childhood infections: a prospective and randomized study. Int J Infect Dis. 2001;5:3-8.
54. American Academy of Paediatrics. Report of the Committee on infectious diseases. Pneumococcal infections. Red Book 2000: 457
55. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998 Jan;26(1):1-10
56. Schrag SJ, Pena C, Fernandez J, Sanchez J, Gomez V, Perez E, Feris JM,Besser RE. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcalcarriage: a randomized trial.JAMA. 2001 Jul 4;286(1):49-56.
57. ISCAP Study Group. Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomized controlled trial. BMJ. 2004;328:791. Epub 2004 Mar 16.
58. World Health Organization. Report of consultative Meeting to Review Evidence and Research Priorities in the Management of Acute Respiratory Infections. Geneva 29 September - 1 October 2003. WHO/FCH/CAH/04.2
59. Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. Lancet 2002; 360:835-841.
60. Pechere JC. Parameters important in short antibiotic courses. J Int Med Res. 2000;28 Suppl 1:3A-12A.
61. Branthwaite A, Pechere JC.Pan-European survey of patients' attitudes to antibiotics and antibiotic use. J Int Med Res. 1996;24:229-38.
62. Fonseca W, Hoppu K, Rey LC, Amaral J, Qazi S. Comparing pharmacokinetics of amoxicillin given twice or three times per day to children older than 3 months with pneumonia. Antimicrob Agents Chemother 2003;47:997-1001.
63. Daschner FD, Behre U, Dalhoff A. Prospective clinical trials of the efficacy of amoxicillin administered twice and four times daily in children with respiratory tract infections. J Int Res 1981; 9: 274-276.
64. Valtonen M, Piipppo, Pitkajarvi ML. Comparison of amoxicillin given two and three times a day in acute respiratory tract infection in children. Scand J Prim Health Care 1986;4:201-4.
65. Cook RC, Zachariah J, Harrison HE. Moderate Lower Respiratory Tract Infection in Children. Br J Clin Pract 1996; 50: 125-8.
66. Co-trimoxazole Amoxicillin Trial In Children Under 5 Years For Pneumonia (CATCHUP Study Group). Clinical efficacy of cotrimoxazole versus amoxicillin twice daily for treatment of pneumonia: A randomized controlled clinical trial in Pakistan. arch Dis Child 2002;86:113-118.
67. World Health Organization. Workshop on the Development of tools to Promote Improved Careseeking. 26-30 July 1999. WHO/FCH/CAH/99.3.
68. Teka T, Dagnew M. Health behavior of rural mothers to acute respiratory infections in children in Gondar, Ethiopia. East Afr Med J 1995;72:623-5.

69. Aguilar, A. M., et al., Mortality Survey in Bolivia: The Final Report: Investigating and identifying the causes of death for children under five, published for the USAID by the Basic Support for Institutionalizing Child Survival (BASICS) Project, Virginia, 1998.
70. Schumacher, R., et al., Mortality Study in Guinea: Investigating the causes of death in children under 5, published by Save the Children and the Basic Support for Institutionalizing Child Survival (BASICS II) Project, Virginia, 2002.
71. World Health Organization, The Multi-Country Evaluation of IMCI Effectiveness, Cost and Impact (MCE) – Progress Report, May 2001-April 2002, WHO/FCH/CAH/02.16, Department of Child and Adolescent Health and Development, WHO, Geneva, 2002.
72. Schellenberg, J. A., et al., Inequities Among the Very Poor: Health care for children in rural southern Tanzania, The Lancet, 2003; 361:561-66.
73. Pandey MR, Daulaire NM, Starbuck ES, Houston RM, McPherson K. Reduction in total under-five mortality in western Nepal through community-based antimicrobial treatment of pneumonia. Lancet. 1991;338: 993-7.
74. Greenwood BM, Greenwood AM, Bradley AK, Tulloch S, Hayes R, Oldfield FS.. Deaths in infancy and early childhood in a well-vaccinated, rural, West African population. Ann Trop Paediatr. 1987;7: 91-9.
75. Reyes H, Perez Cuevas R, Salmeron J, Tome P, Guiscafre H, Gutierrez G. Infant mortality due to acute respiratory infections: the influence of primary care processes. Health Policy and Planning. 1997;12:214-23.
76. Mirza NM , Macharia WM , Wafula EM , Agwanda R , Onyango FE. 1990. Mortality patterns in a rural Kenyan community. East Afr Med J 1990;67:823-9.
77. Snow RW, Schellenberg JR, Forster D, Mung'ala VO, Marsh K. Factors influencing admission to hospital during terminal childhood illnesses in Kenya. Int J Epidemiol. 1994;23:1013-9.
78. Katende C. The impact of accessibility to health facilities on infant and child mortality in rural Uganda. [Unpublished] 1994. Presented at the Annual Meeting of the Population Association of America, Miami, Florida, May 5-7, 1994. 37.
79. Molbak K, Aaby P, Ingholt L, Hojlyng N, Gottschau A, Andersen H, Brink L, Gansted U, Permin A, Vollmer A. Persistent and acute diarrhoea as the leading causes of child mortality in urban Guinea Bissau. Trans Roy Soc Trop Med Hyg. 1992;86:216-20.
80. Sodemann M, Jakobsen MS, Molbak K, Alvarega IC, Aaby P. High mortality despite good care-seeking behavior: A community study of childhood deaths in Guinea Bissau. Bull World Health Organ.1997; 75:205-12.
81. Murray J, Newes Adeyi G, Graeff J, Fields R, Ramuson M, Salgado R, Sanghvi T. Emphasis behaviours in Maternal and Child Health: Focusing on Caretaker behaviors to Develop maternal and Child health Programs in Communities. USAID, BASICS. 1997.
82. de Silva MW; Wijekoon A; Hornik R; Martines J. Care seeking in Sri Lanka: one possible explanation for low childhood mortality. Social Science and Medicine. 2001 Nov;53(10):1363-72.
83. Terra de Souza AC, Peterson KE, Gardener J, Andrade MF, Ascheiro A. The circumstances of post neonatal death in Ceara, north Eastern Brazil; Mothers health are-seeking behavior during infants' fatal illness. Soc Sci Med.2000;51:1675-93.
84. Sutrisna B, Reingold A, Kresno S, Harrison G, Utomo B. Care-seeking for fatal illnesses in young children in Idramayu, West Java, Indonesia. Lancet 1993;25 342(8874):787-9.
85. Mtango FD, Neuvians D Acute respiratory infections in children under five years. Control project in Bagamoyo District, Tanzania. Trans R Soc Trop Med Hyg 1986;80:851-8.
86. Datta N, Kumar V, Kumar L, Singhi S.Application of case management to the control of acute respiratory infections in low-birth-weight infants: a feasibility study. Bull World Health Organ 1987;65:77-82.
87. Bang AT, Bang RA, Tale O, Sontakke P, Solanki J, Wargantiwar R, Kelzarkar. Reduction in pneumonia mortality and total childhood mortality by means of community-based intervention trial in Gadchiroli, India. Lancet 1990;28;336:201-6.
88. Khan AJ, Khan JA, Akbar M, Addiss DG. Acute respiratory infections in children: a case management intervention in Abbottabad District, Pakistan. Bull World Health Organ 1990;68:577-85.
89. Fauveau V, Stewart MK, Chakraborty J, Khan SA. Impact on mortality of a community-based programme to control acute lower respiratory tract infections. Bull World Health Organ 1992;70:109-16.
90. Sazawal, S. and R. E. Black, Effect of Pneumonia Case Management on Mortality in Neonates, Infants, and Preschool Children: A metaanalysis of community-based trials, The Lancet Infectious Diseases, vol. 3, no. 9, September 2003, pp. 547-556.

91. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS; Bellagio Child Survival Study Group. How many child deaths can we prevent this year? Lancet. 2003;362:65-71
92. World Health Organization. Millennium development Goals. http://www.who.int/mdg/goals/MDGsList_smartformat.pdf (accessed on 16.9.04)
93. WHO/UNICEF Joint Statement. Management of pneumonia in community settings. The United Nations Children's Fund/World Health Organization, Geneva/NewYork 2004. WHO/FCH/CAH/04.06 or UNICEF/PD/Pneumonia/01
94. Khan M.A., Qazi S.A. and Rehman G.N. A community study of the application of WHO ARI management guidelines in Pakistan. Ann Trop Paed 1993;13:73-78.
95. Rodewald LE, Pichichero ME. Compliance with antibiotic therapy; a comparison of deuterium oxide tracer, urine bioassay, bottle weights and parental reports. J. Pediatr 1993;123:143-147.
96. Dixon, W.J., Massey, F.J. Introduction to Statistical Analysis. 4th Edition McGraw-Hill (1983) pp. 105-107.
97. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. Annals of Internal Medicine. 118(3):201-10, 1993 Feb 1.
98. WHO Technical Report Series No 850, 1995, Annex 3 pp. 97-137