INTRODUCTION

Respiratory infections (RIs) are the most common problems in paediatric clinical practice; they can be classified into upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs). The upper respiratory tract consists of the airways from nostrils to vocal cords in the larynx, including paranasal sinuses and middle ear. The lower respiratory tract covers the continuation of the airways from trachea and bronchi to bronchioles and alveoli. RIs are not confined to the respiratory tract and have systemic effects because of possible extension of infection or microbial toxins, inflammation, and reduced lung function. Diphtheria, pertussis (whooping cough), and measles are vaccine-preventable diseases that may affect respiratory tract component along with other systems.

Except during the neonatal period, RIs are the most common causes of both illness and mortality in children under the age of five, who average three to six episodes of RIs annually regardless of the economic and geographic situation. However, the proportion of mild-to-severe disease varies between high- and low-income countries, and because of the differences in specific aetiologies and risk factors, the severity of LRTIs in children under the age of five is worse in developing countries, resulting in a higher case fatality rate. Although medical care to some extent can mitigate both severity and fatality, many severe LRTIs do not respond to the therapy, largely because of the lack of highly effective antiviral drugs. Around 10.8 million children die each year, and according to the World...
Health Organization (WHO) an estimated 2 million children under the age of five die of pneumonia.4

CAUSES OF RIs AND THE BURDEN OF DISEASE

RIs in children take a heavy toll on life, especially where medical care is not available or is not sought.

Upper Respiratory Tract Infections

URTIs, such as rhinitis (common cold), sinusitis, ear infections, acute pharyngitis or tonsilopharyngitis, epiglottitis, and laryngitis, are the most common infectious diseases in children. Ear infections and pharyngitis may lead to severe complications of deafness and acute rheumatic fever, respectively.

Majority of the URTIs are caused by viruses. Rhinoviruses account for 25% to 30% of URTIs; respiratory syncytial viruses (RSVs), parainfluenza, influenza viruses, human metapneumovirus, and adenoviruses 25% to 35%; coronaviruses 10%; and unidentified viruses for the remainder.5 Because most URTIs are self-limiting, their complications are more important than the infections. Acute viral infections predispose children to bacterial infections of the sinuses and middle ear,6 and aspiration of the infected secretions and cells may result in LRTIs.

Acute Pharyngitis: Acute pharyngitis is caused by viruses in more than 70% of cases in young children. Mild pharyngeal redness, swelling, and tonsil enlargement are the typical symptoms. Streptococcal infection is rare in children under the age of five and more common in older children. In countries with unsophisticated living conditions and populations that may have a genetic predisposition, poststreptococcal sequelae such as acute rheumatic fever and carditis are common in school-age children and may also occur in children under the age of five. In developing countries, acute pharyngitis in conjunction with the appearance of white or yellow spots on the back of the throat is nearly always caused by Corynebacterium diphtheriae. However, with the almost universal vaccination of infants with DTP (diphtheria-tetanus-pertussis) vaccine, diphtheria is rare.

Acute Ear Infection: Acute ear infection occurs in up to 30% of the URTIs. In developing countries with inadequate medical care, it may lead to perforated eardrums and chronic ear discharge in late childhood and ultimately to hearing impairment or deafness.7 Chronic ear infection following repeated episodes of acute ear infection is common, affecting 2% to 6% of school-age children and may be disabling and affect learning in them. Repeated ear infections may lead to mastoiditis, which in turn may spread infection to the meninges. Mastoiditis and other complications of URTIs account for nearly 5% of all the deaths from acute respiratory infection (ARI), worldwide.8

Lower Respiratory Tract Infections

The common LRTIs in children are pneumonia and bronchiolitis. Respiratory rate is a valuable clinical sign for the diagnosis of acute LRTI in children with symptoms of coughing and rapid breathing. Severe cases of the disease can be identified by the presence of lower chest wall indrawing.9,10 Currently, the most common causes of viral LRTIs are RSVs. They tend to be highly seasonal unlike the parainfluenza viruses, the next most common cause of viral LRTIs. The epidemiology of influenza viruses in children in developing countries deserves urgent attention. Measles virus was the most important viral cause of respiratory tract-related morbidity and mortality in children in developing countries before the availability of measles vaccine.

Pneumonia: Pneumonia can be caused by both bacteria and viruses. Bacterial pneumonia is often caused by Streptococcus pneumoniae (pneumococcus) or Haemophilus influenzae, mostly type B (Hib),
and occasionally by *Staphylococcus aureus* or other streptococci.

Only about 8 to 12 of the many types of pneumococcus cause most cases of bacterial pneumonia, although the specific types may vary between adults and children and among different geographic locations. Other pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, cause atypical pneumonias, but their aetiological role in children under the age of five in developing countries is unclear.

The burden of LRTIs caused by Hib or *S. pneumoniae* is difficult to determine because current techniques to establish bacterial aetiology lack sensitivity and specificity. Results of pharyngeal cultures do not always reveal the pathogen that is the cause of the LRTI. Bacterial cultures of lung aspirate specimens are often considered the gold standard, but they are not practical for field application. Review of several studies indicates that *S pneumoniae* and Hib account for 13% to 34% and 1.4% to 42% of bacterial pneumonia, respectively, whereas the other few studies suggest that Hib accounts for 5% to 11% cases of pneumonia.11-14 Reduced levels of clinical or radiological pneumonia in clinical trials of a nine-valent pneumococcal conjugate vaccine provide an estimate of the vaccine-preventable disease burden (valency indicates the number of serotypes against which the vaccine provides protection; conjugate refers to conjugation of polysaccharides to a protein backbone). In a study conducted in Gambia, 37% of radiological pneumonia was prevented.15

Upper respiratory tract colonization with potentially pathogenic organisms and aspiration of the contaminated secretions has been implicated in the pathogenesis of bacterial pneumonia in young children. Infection of the upper respiratory tract with influenza virus or RSVs has been shown to increase the binding of both *H influenzae*16 and *S pneumoniae*17,18 to the cell linings of the nasopharynx. This finding may explain why increased rates of pneumococcal pneumonia parallel influenza and RSV epidemics. A study in South Africa showed that vaccination with a nine-valent pneumococcal conjugate vaccine reduced the incidence of hospitalisation due to virus-associated pneumonia by 31%, suggesting that pneumococcus plays an important role in the pathogenesis of virus-associated pneumonia.19

Entry of bacteria from the gut and its spread to the lungs through the bloodstream has also been proposed for the pathogenesis of Gram-negative organisms,20 but such bacteria are uncommon aetiological agents of pneumonia in immune-competent children. However, in neonates and young infants, Gram-negative pneumonia is not uncommon (Quiambao forthcoming).

Viruses are responsible for 40% to 50% of infection in infants and children hospitalised for pneumonia in developing countries.21-23 Measles virus, RSVs, parainfluenza viruses, influenza type A virus, and adenoviruses are the most important causes of viral pneumonia. Radiographic differentiation between viral and bacterial pneumonias is difficult, partly because the lesions look similar and partly because bacterial superinfection occurs with influenza, measles, and RSV infections.24 In developing countries, the case-fatality rate in children with viral pneumonia ranges from 1% to 7.3%,22,25 bacterial pneumonia from 10% to 14%, and mixed viral and bacterial infections from 16% to 18%.24,26

Influenza: Even though influenza viruses usually cause URTIs in adults, they are increasingly being recognized as an important cause of LRTIs in children and perhaps the second most important cause after RSVs for the hospitalisation of children with ARI.27 Although influenza is considered infrequent in developing countries, its epidemiology remains to be investigated thoroughly. The potential burden of influenza as a cause of death in children is unknown.
Influenza virus type A may cause seasonal outbreaks, and type B may cause sporadic infection. Recently, avian influenza virus has caused infection, disease, and death in small numbers of individuals, including children, in a few Asian countries. Its potential for emergence in human outbreaks or a pandemic is unknown, but it could have devastating consequences in developing countries and could pose a threat to health worldwide. New strains of type A viruses will almost certainly arise through mutation, as in the case of Asian and Hong Kong pandemics in 1950s and 1960s.

**CASE MANAGEMENT**

The simplification and systematisation of case management for early diagnosis and treatment of RIs have enabled significant reductions in mortality in developing countries, where access to pediatricians is limited. The WHO clinical guidelines for RI case management (WHO 1991) use 2 key clinical signs: respiratory rate, to distinguish children with pneumonia from those without, and lower chest wall indrawing, to identify severe pneumonia requiring referral and hospital admission. Children with audible stridor when calm and at rest or with danger signs of severe disease such as inability to feed also require referral. Children without these signs are classified as having an ARI but not pneumonia.

Children showing only rapid breathing are treated for pneumonia with outpatient antibiotic therapy. Children who have a cough for more than 30 days are referred for further assessment of tuberculosis and other chronic infections.

**Septilin Syrup in the Management of Respiratory Diseases**

Septilin possesses immunomodulatory and anti-inflammatory properties, which potentiate the nonspecific immune responses of the body. Septilin stimulates phagocytosis by macrophage activation, increases the number of polymorphonuclear cells, and helps overcome infection. Septilin builds up resistance to infection and prevents reinfection. Septilin’s stimulatory effect on the humoral immunity increases the antibody forming cells, thereby increasing the secretion of antibodies into the circulation. The composition of Septilin Syrup is summarized in Table 1.

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<th>Table 1. COMPOSITION (Each 5 ml of Septilin syrup contains active ingredients of)</th>
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<tr>
<td><strong>Pdrs.</strong></td>
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<tr>
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Influenza virus type A may cause seasonal outbreaks, and type B may cause sporadic infection. Recently, avian influenza virus has caused infection, disease, and death in small numbers of individuals, including children, in a few Asian countries. Its potential for emergence in human outbreaks or a pandemic is unknown, but it could have devastating consequences in developing countries and could pose a threat to health worldwide. New strains of type A viruses will almost certainly arise through mutation, as in the case of Asian and Hong Kong pandemics in 1950s and 1960s.

**PHARMACOLOGY**

Commiphora mukul shows a wide range of inhibiting activity against both Gram (+) and Gram (-) bacteria. Maharasnadi quath has analgesic, antiphlogistic, and antipyretic properties.

T cordifolia reduces IL-1β production and inhibits TNF-a, and hence, is a potent anti-inflammatory agent. T cordifolia reverses chemically induced immunosuppression providing the immunomodulatory support. It has potent immunomodulatory and
immunostimulatory activities, which increase the levels of antibodies and activate macrophages.\textsuperscript{32,33}

\textbf{R cordifolia} has immunomodulatory effect, which occurs through the suppression of iNOS protein.\textsuperscript{34}

\textbf{E officinalis} has immunomodulatory and antibacterial activities against test bacteria.\textsuperscript{35,36}

\textbf{G glabra} has anti-inflammatory action similar to hydrocortisone and other corticosteroid hormones.\textsuperscript{37} It also enhances immunostimulation.\textsuperscript{38}

\textbf{Trikatu} is an ayurvedic formulation comprising a 1:1:1 ratio of dried fruits of \textit{Piper nigrum} and \textit{Piper longum} and dried rhizomes of \textit{Zingiber officinale}.\textsuperscript{39}

The essential oil from \textit{S lappa} root exhibits strong antiseptic and disinfectant activity against streptococcus and staphylococcus. The root shows astringent and antiseptic activities.\textsuperscript{40}

In order to evaluate the efficacy of Septilin syrup in children, several controlled clinical trials have been conducted.

\textbf{Clinical Trial 1}

Evaluation of the immunomodulatory efficacy and safety of Septilin syrup, as an adjunct in solid malignancy paediatric patients on chemotherapy: A prospective, randomized, controlled, phase III clinical trial.

\textbf{Aim}

The aim of the study was to evaluate the immunomodulatory efficacy and the short- and long-term safety of Septilin syrup, as an adjunct, in pediatric solid malignancy patients undergoing chemotherapy.

\textbf{Patients and Methods}

\textbf{Inclusion criteria}

Pediatric patients with FNAC-confirmed diagnosis of advanced solid malignancy (Wilms` tumor and neuroblastoma) and whose parents/guardians were willing to give informed written consent were included in the study.

\textbf{Exclusion criteria}

Patients requiring immediate blood transfusion and whose parents were unwilling to give informed written consent were excluded from the study.

\textbf{Study procedure}

Informed written consent was obtained from the parents/guardians of all the 38 patients included in the study. Each patient’s demographic characteristics and a detailed medical history were recorded in a structured case report form. All enrolled patients were randomly divided into 2 groups with the help of a computerised random number generator program. All patients from the Septilin group received Septilin (5 ml, thrice daily), for 6 weeks, starting 48 hours prior to the commencement of chemotherapy, whereas the other group received chemotherapy alone. Chemotherapy protocol included injections Vincristine-1.5 mg/mm\textsuperscript{2}, Actinomycin D-15 µg/kg, and Adriamycin-60 mg/mm\textsuperscript{2}.

\textbf{Results}

Results of the study showed a significant increase in the levels of IgG, IgM, and IgA in patients suffering from Wilms’ tumor and neuroblastoma. There were no incidences of any adverse effects and only a minimal loss of appetite was observed in the Septilin-treated group patients.

\textbf{Conclusion}

Patients in the Septilin-treated group had reduced incidence of adverse events, minimal loss of appetite, and absence of leukopenia at the end of the treatment. Overall, patients treated with Septilin and chemotherapy responded better clinically,
as evident by the significant tumor regression, compared to the patients treated with chemotherapy alone.

Clinical Trial 2
Comparative evaluation of the efficacy and safety of “Septilin syrup” with prophylactic antibiotics, in preventing postoperative infections in children

Aim
The aim of the study was to comparatively evaluate the safety and efficacy of “Septilin syrup” with prophylactic antibiotics, in preventing postoperative pediatric infections, during elective surgery in children.

Patients and Methods
Inclusion criteria
Children of either sex, who had been admitted for elective surgery, and whose parents were willing to give written informed consent were included in the study.

Exclusion criteria
Children with renal, hepatic, or cardiac impairment and whose parents were unwilling to give written informed consent were excluded from the study.

Study procedure
All the 50 enrolled children were randomly allocated into two groups of 25 each (“Septilin syrup” group and “other drugs” group). All the children underwent preoperative clinical and laboratory investigations. Children in the “Septilin syrup” group were administered 5 ml of Septilin syrup on the morning of the surgery and the syrup was continued at the same dosage, twice daily, during the first postoperative week. In the “other drugs” group, all the children were administered injection Ceftriaxone (50 mg/kg), at the time of induction of anesthesia, which was followed by oral antibiotics during the first postoperative week.

Results
Results of the study showed that there was no incidence of postoperative surgical wound infection in both the groups. However, high fever and URTI were reported in the “other drugs” group; no such complaints were reported in the “Septilin syrup” group. Also, there were no complaints of anorexia, severe nausea, and vomiting in the Septilin-treated group. There was also an increase in the levels of IgG in the “Septilin syrup” group. Overall, children in the “Septilin syrup” group had a smoother clinical recovery as compared to the children in the “other drugs” group. Also, there were no other clinically significant adverse reactions, either observed by investigators, or reported by patients, in the “Septilin syrup” group, till the end of the study.

Conclusion
None of the patients in both groups developed wound infection; patients in the “Septilin syrup” group had a much smoother clinical recovery as compared to the children in the “other drugs” group. No clinically significant adverse reactions were observed in the patients treated with Septilin, which confirms its safety. Therefore, it may be concluded that, Septilin syrup is safe and equally effective alternative method to prophylactic antibiotic therapy in preventing postoperative infections during elective surgery in children.

Clinical Trial 3
Evaluation of the efficacy of Septilin in persistent low-grade infections in school-age children: A placebo-controlled study

Aim
The aim of the study was to evaluate the efficacy of
Septilin in persistent low-grade infections in school-age children.

**Patients and Methods**

**Inclusion criteria**

Children of both sexes who were in the age group of 6-10 years, diagnosed with URTI and ENT infections, and willing to sign informed consent were included in the study.

**Exclusion criteria**

Children who were not having persistent infection and were unwilling to give informed consent were excluded from the study.

**Study procedure**

All the 42 enrolled children suffering from persistent low-grade infection were divided into 2 groups of 21 students each. Group “A” received Septilin syrup and Group “B” received a similar placebo at a dosage of 1 tablespoonful twice a day for 3 months. Hemoglobin and complete blood counts of both the groups were performed and repeated after 3 months. ENT examinations were done at intervals of one month for duration of three months.

**Results**

Sixteen of 21 students in Group “A” (Septilin) showed excellent results both clinically and symptomatically. Overall improvement was observed and there was no recurrence of symptoms in this group. In the placebo group, no significant change was observed either symptomatically or clinically. The infection persisted. Except for minor GI disturbances and glossitis in 2 cases, Septilin was well-tolerated.

**CONCLUSION**

It can be concluded from the above study that Septilin is effective in the treatment of persistent upper respiratory tract and ENT infections.

**Status of Septilin in RI**

The results from the clinical trials have proved that Septilin syrup is effective in the management of URTI and LRTI. The effects of Septilin syrup may be due to the synergistic action of all the herbs present rather than a single herb alone. The constituents act in a synergistic, complementary manner to potentiate the therapeutic effects of Septilin syrup. Its immunomodulatory activity is highly beneficial in preventing recurrent infection. Septilin syrup is found to significantly reduce URTI, increase immunity, and prevent the body from reinfection in infants with RTI and ENT infections, as reported in the above three clinical trials. It can also be used along with other medications. No adverse effects were reported in patients treated with Septilin. It is safe for long-term use and has no contraindications. Thus, Septilin is a safe, effective, practical, and affordable therapeutic modality for URTI.

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**REFERENCES**

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