LOWER RESPIRATORY INFECTIONS IN CHILDREN

New Pathogens, Old Pathogens and The Way Forward

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19 APRIL 2013

Dewan Kuliah Utama (DKU)
Fakulti Perubatan dan Sains Kesihatan
Universiti Putra Malaysia

Universiti Putra Malaysia Press
Serdang • 2013
http://www.penerbit.upm.edu.my

First Print 2013

UPM Press is a member of the Malaysian Book Publishers Association (MABOPA)
Membership No.: 9802

Typesetting : Sahariah Abdol Rahim @ Ibrahim
Cover Design : Md Fairus Ahmad

Design, layout and printed by
Penerbit Universiti Putra Malaysia
43400 UPM Serdang
Selangor Darul Ehsan
Tel: 03-8946 8855 / 8854
Fax: 03-8941 6172
http://www.penerbit.upm.edu.my

Contents

OVERVIEW

Lower respiratory infections (LRI) , refer to a broad category of diseases , that involve the lower respiratory tract which comprises the trachea (wind-pipe), bronchial tubes, bronchioles or lungs.

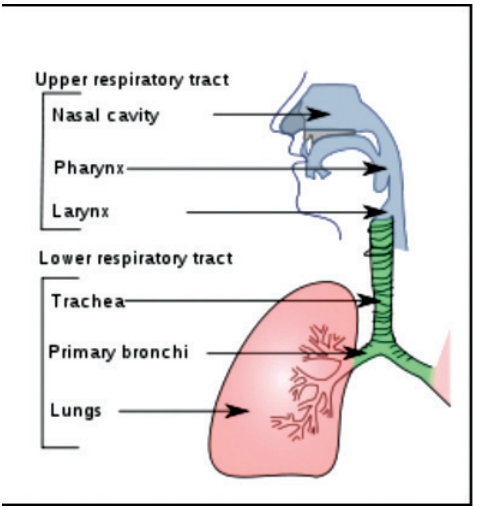

Figure 1 Respiratory Tract

Examples of LRI are pneumonia, bronchitis, bronchiolitis and croup. Croup, which is an illness of the larynx (upper respiratory region), is considered an LRI as consequences of its infection often spread to the lower respiratory tract.

LRI is a major threat to children's health everywhere as children are the most susceptible group infected (Brodzinki H, 2009).It is reported that the highest incidence of respiratory infection occurs during the first year of life, where infants and children less than five years of age would experience 3 – 11 episodes of acute respiratory infection. Ninety-eight percent of all respiratory death is related to

infection of the lower respiratory tract: 42 % of these deaths are due to pneumonia occurring in children less than 5 years of age. Out of these childhood deaths, 95% occur among children living in the less developed parts of the world. The situation is dire in these regions as poor nutrition is prevalent and access to health care is scare or limited. It remains the common cause for emergency department visits and hospitalization (Osterhaus AD, 2008). As such, it is the number one cause of death in the developing world.

For treatment purpose of each of these illnesses, it is important at the onset to identify the causative agent of the infection. For example, in pneumonia, it is important to differentiate viral or bacterial infection. Of bacterial infection, it could be due to *Streptococcus pneumoniae, Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococus pyrogenes*. If a viral infection is suspected, of which it could be Respiratory syncytial virus (RSV), metapneumovirus, parainfluenza, or adenovirus, then no antibiotics is administered since such prescription would not have any effect on virus. This is also to prevent resistance of antibiotics by organisms, to reduce overall reduction of antibiotics use and lastly to control any infection during hospital stay or nosocomial transmission. (Pavia AT et al, 2011).

The next section would look at the specific illness of each of the above LRI, that being, pneumonia, bronchiolitis, bronchitis and croup respectively.

PNEUMONIA

Pneumonia is a common infection that affects many infants (young children between the ages of 1 month to 12 months) and children. According to the World Health Organization (WHO), over two million children die from this infection each year (Rec, 2007). In 2008, pneumonia killed more children than other diseases, measles, malaria and Aids, combined. Pneumonia accounts for one out of five under five deaths in the developing world. It is the third leading cause of death accounting for over 1.9 million deaths annually in children below 5 years of age. Worldwide, pneumonia accounts for 19 percent of all under five deaths where 26 % of this is of neonatal deaths (Bull, 2008).

The lungs are composed of thousands of tubes (bronchi) that are subdivided into smaller airways (bronchioles), which end in these small sacs, alveoli (Figure 2). The alveoli contain capillaries where oxygen is added to the blood and carbon dioxide is removed.

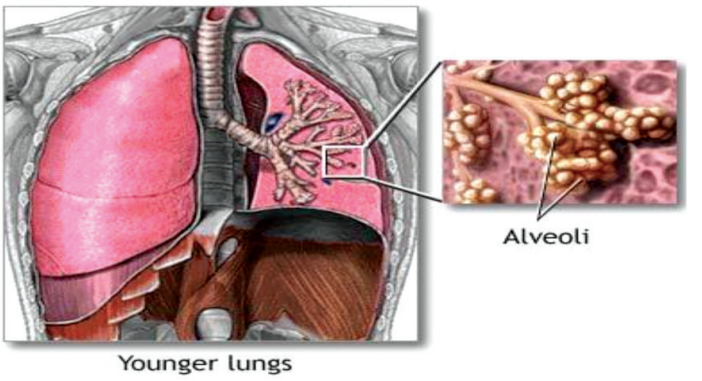

Figure 2 Pneumonia affects the alveoli

When a person has pneumonia, pus and fluid fill the alveoli in one or both lungs, which interfere with oxygen absorption, making

breathing difficult. This condition will result in the inflammation of the lungs affecting the microscopic small air sacalveolars. Most acute respiratory infections result in mild illnesses, such as the common cold. But in vulnerable children, infections that begin with mild symptoms may sometimes lead to more severe illnesses, such as pneumonia – especially when they coincide with other illnesses like diarrhea and malaria.

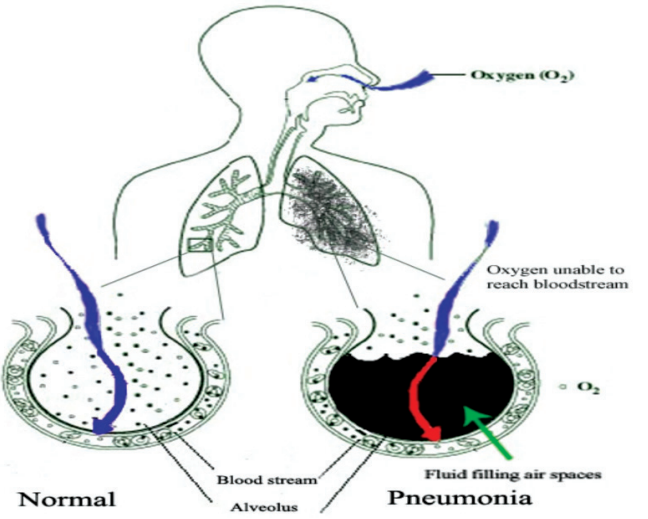

Figure 3 Differences between a normal alveolar and pneumonia infected

How is Pneumonia Transmitted?

Children are susceptible to infection when they have weak immunity system (as in immunocompromised patients). However, in a community –acquired pneumonia, children are infected via air-borne or aerosol droplets or through contact (fomites).

Multiple microbes cause LRI in infants and children, and establishing microbial diagnosis is difficult. In children, 85 % is caused by co-infection of bacteria and viruses. Investigations to detect the etiology involved performing multiple laboratory tests, some only available in research laboratories. For some organisms, particularly viruses, Mycoplasma and chlamydiaceae, microbial etiology is inferred by detection of microorganisms in the upper respiratory tract. For others, serologic tests or nucleic assay (polymerase chain reaction) is the preferred method. Certain bacteria are present as the normal upper respiratory flora. Bacteremia (presence of bacteria in blood) confirms the cause but is present in only 1-10% of hospitalized children with pneumonia. In most cases, extensive or invasive testing is not warranted. Among the viruses the most common is RSV. The leading cause of pneumonia in children of the developing countries is *S.pneumoniae* followed by another bacterial pathogen, *Hinfluenzae type b (Hib*). With the introduction of *Hib* vaccine in the 1990's, Hib cases have been on the decline. Clinical presentations and agents of pneumonia in infants and children differ from adults. As shown in the following table (Table 1), there are various microbes causing pneumonia.

Table 1 Microbial Causes of Community-Acquired Pneumonia in Childhood

Age	Etiologic agents	Clinical Features
Birth – 3 wks (Neonates-age less than one-month old)	Group B Streptococus	Part of early-onset septicemia; usually severe
	Gram-negative enteric bacilli	Frequently nosocomial; occurs infrequently within 1 week of birth
	Cytomegalovirus	Part of systemic cytomegalovirus infection. Part of early-onset septicemia
	Listeria monocytogenes	Part of disseminated infection
	Herpes simplex virus	Part of congenital syndrome
	Treponemapallidum	From maternal genital infection: afebrile pneumonia
	Genital Mycoplasma or Ureaplasma	From maternal genital infection: afebrile,subacute, interstitial pneumonia
3 wks-3 mths (Infants)	*Chlamydia trachomatis*	From maternal genital infection ; afebrile, subacute, interstitial pneumonia
	Respiratory syncytial virus (RSV)	Peak incidence at 2-7 months of age; usually wheezing illness (bronchiolitis/pneumonia)
	Parainfluenzaviruses,especially type 3	Similar to RSV, but slightly older infants and not epidemic in winter
	Streptococuspneumoniae	Most common cause of bacterial pneumonia
	Bordetella pertussis	Primarily causes bronchitis; secondary bacterial pneumonia and pulmonary hypertension can complicate severe cases

3 mths – 5 yrs (Children)	RSV, parainfluenza, influenza, metapneumovirus,adenovirus,rhinovirus	Most common cause of pneumonia
	Streptococcus pneumoniae	Most likely cause of lobar pneumonia; incidence may be decreasing after vaccine use.
	Haemophilusinfluenzae	Type b uncommon with vaccine use; non-typable stains cause pneumonia in immunocompromised hosts and in developing countries
	Staphylococcus aureus	Uncommon, although community acquired (CA)-MRSA is becoming more prevalent
	Mycoplasma pneumoniae	Causes pneumonia primarily in children over 4 years of age.
	Mycobacterium tuberculosis	Major concern with children of high prevalence and in children with HIV
5-15 yrs (Children-Adolescent)	*Mycoplasma pneumoniae*	Major cause of pneumonia ,variable chest-xray appearance
	Chlamydophilapneumoniae	Controversial, but probably an important cause in older children in this age group

Some believe that common bacterial pathogens causing pneumonia are often already present in a child's nose or throat (this is referred as colonization in medical term) and are then inhaled into the lungs, causing infection. Pathogens may also be spread through contaminated air droplets or may result from blood-borne infections. During or shortly after birth, babies are at higher risk of developing pneumonia from coming into contact with organisms in the birth canal or from contaminated substances contacted during delivery.

Children with pneumonia may have a range of symptoms depending on their age and the cause of the infection. Bacterial pneumonia usually causes children to become severely ill with high fever and rapid breathing. Viral infections, however, often come on gradually and may worsen over time.

Some common symptoms of pneumonia in children and infants include rapid or difficult breathing, cough, fever, chills, headaches, loss of appetite and wheezing. Children under five with severe cases of pneumonia may struggle to breathe, with their chests moving in or retracting during inhalation (known as 'lower chest wall in drawing'). Young infants may suffer convulsions, unconsciousness, hypothermia, lethargy and feeding problems.

Since it is difficult to prove the etiological agent of LRI, antimicrobial therapy is empiric. As viral LRI is more frequent in healthy children, no antibiotic is given unless otherwise proven. In neonates, antibiotic such as cefotaxime is administered since the pathogens are similar to that of sepsis. The use of antiviral therapy depends on pathogens, the severity of the clinical course and the availability of effective non- toxic therapy.

Vaccines may help prevent pneumonia in children and this depends on the pathogen. Ribavirin has been given to some children younger than 24 months to prevent pneumonia caused

by RSV though its use has been questioned. Flu vaccine prevents pneumonia and other problems caused by the influenza virus. This influenza vaccine must be given each year to protect against new virus strains. Hib vaccine prevents pneumonia in children from *Hib.* Pneumococcal vaccine prevents pneumonia from *S. pneumoniae*.

BRONCHIOLITIS

Bronchiolitis is an acute infectious disease of the lower respiratory tract that occurs primarily in young infants, most often in those aged 2-24 months. Day-care attendance and exposure to cigarette smoke can increase the likelihood of an infant to develop bronchiolitis.

Among the developed countries, the frequency of bronchiolitis appears to be similar. However epidemiologic data for underdeveloped countries is incomplete. Peak incidence of bronchiolitis usually occurs during winter months in temperate climates and during the rainy season in tropical climates. RSV infection is most widespread during the winter. The number of cases of bronchiolitis occurring during summer and early fall is less and they are more likely caused by rhinovirus or parainfluenza virus.

Eighty percent of bronchiolitis are due primarily to RSV, the most common pathogen worldwide. More than half of all infants are exposed to this virus by their first birthday. Other common viruses that can cause bronchiolitis include adenovirus, human metapneumovirus, influenza and parainfluenza virus type 3. The less common causes include *B. pertussis, M.pneumoniae*, measles, influenza and adenovirus. Adenovirus has been associated with a severe form of bronchiolotis, bronchiolitis obliterans.

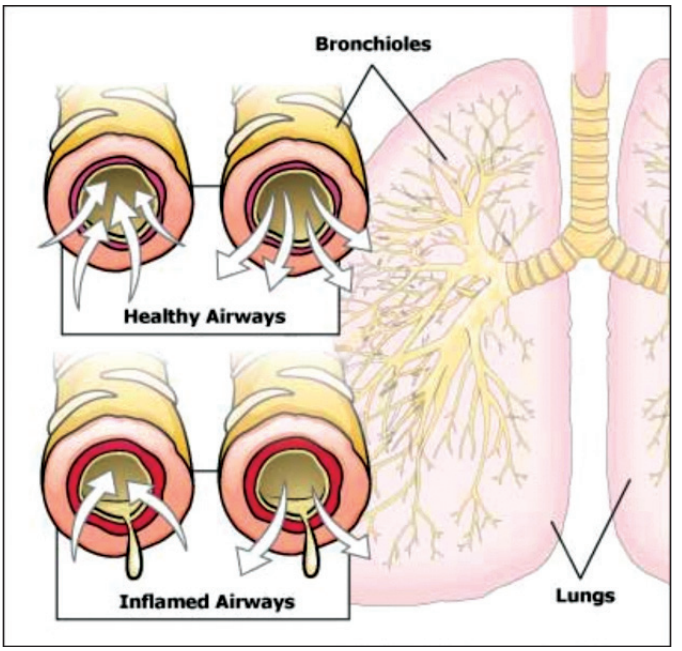

Figure 4 In bronchiolitis, the airway becomes obstructed from swelling of the bronchiole walls

Bronchiolitis causes the inflammation (swelling) of the bronchioles, the smallest passage of the lungs (Figure 4). Infants are more likely to be infected as their airways are smaller than the older children and so are more easily blocked. The swollen bronchioles, filled with mucus, will obstruct the airway passage and these results in the symptoms it presents: coughing, wheezing and shortness of breath.

Bronchiolitis represents itself as late stage of respiratory disease that progresses over several days. Upper respiratory tract infection consists of nasal discharge and mild cough about 3 – 5 days. This infection will progress to spread to the lower respiratory tract via

infected epithelial cells or cell to cell spread. Infection at the lower tract is marked by shortness of breath, cough, wheezing, crackles and nasal flaring.

The viral infection will cause alteration of epithelial cells and mucosal surfaces of the respiratory tract. Earliest lesion is observed 18 – 24 hours after the onset of the disease. Lesions consist of bronchiolar cell necrosis, ciliary disruption and peribronchiolar infiltration with lymphocytes. Terminal bronchiolar epithelial cells are targets for viral infection and are damaged by direct viral invasion. Infants who are premature, those who suffer from congenital heart diseases and infection of chronic disease are susceptible. Examination may reveal wheezing and crackling sounds heard through stethoscope examination of the chest. Tests that may be done include blood gases, chest x –ray and a culture of a sample of nasal fluid to determine the virus causing the disease. Antibiotics do not work against viral infections. Sometimes, no treatment is necessary. Most medications do not help to treat bronchiolitis. To date, there is no RSV vaccine available. Anti-viral drug ribavirin is ineffective. Careful hand washing can prevent the spread of the infection

BRONCHITIS

Bronchitis is an infection of older adolescents. It is an inflammation of the lining of the bronchial tubes, the main airways that connect the trachea (windpipe) to the lungs. This delicate, mucus-producing lining covers and protects the respiratory system, the organs and tissues involved in breathing.

With bronchitis, it may be harder for air to pass in and out of the lungs, the tissues become irritated, and more mucus is produced. The most common symptom of bronchitis is cough. When you breathe in (inhale), small, bristly hairs near the openings of your nostrils

filter out dust, pollen, and other airborne particles. Particles that slip through become attached to the mucus membrane, which has tiny, hair-like structures called cilia on its surface. But sometimes the pathogens get through the cilia and other defense systems in the respiratory tract and this can cause illness.

Bronchitis can be acute or chronic. Most people have acute bronchitis at some point in their lives. An **acute** medical condition comes on quickly and can cause severe symptoms, but it lasts only a short time (no longer than a few weeks). Virus causes about 90 % of acute bronchitis whereas bacteria are fewer than 10 %. The viruses are rhinoviruses, adenovirus, influenza and recently the new emerging metapneumovirus. These viruses infect the respiratory tract and attack the bronchial tubes. Acute bronchitis caused by non-viruses pathogens are *M. pneumoniae, C. pneumoniae, B. pertussis* and *B. parapertussis.*.

In acute bronchitis, these pathogens will infect the epithelium of the bronchi, resulting in its inflammation (swollen) and the increase production of the mucus. Cough, the most common symptom, is a natural mechanism to remove the excess mucus form the lungs. Other symptoms include sore throat, runny nose, nasal congestion, fever, fatigue and the production of sputum.

Chronic bronchitis, a disorder in adults, on the other hand, can be mild to severe and is longer lasting — from several months to years. With chronic bronchitis, the bronchial tubes continue to be inflamed (red and swollen), irritated, and produce excessive mucus over time. The most common cause of chronic bronchitis is smoking. Bacterial superinfection by organisms colonizing the upper respiratory tract is more likely in these patients. People who have chronic bronchitis are more susceptible to bacterial infections of the airway and lungs, like pneumonia. In some people with

chronic bronchitis, the airway becomes permanently infected with bacteria. Pneumonia is more common among smokers and people who are exposed to secondhand smoke.

Since the causative agent is most likely virus, antibiotics are not prescribed. Treatment of bronchitis is more symptomatic and palliative. Expectorant and antihistamines have not been proven to be effective. Antiviral therapy for influenza infection is given early in the course of the disease. Bronchitis due to *M.pneumoniae* or *C.pneumoniae* can be treated with macrolide antibiotic but therapeutic benefit is not proven for bronchitis.

CROUP

Croup is a condition that causes an inflammation of the upper airways — the voice box (larynx) and windpipe (trachea). It often leads to a barking cough or hoarseness, especially when a child cries.

Most cases of croup are caused by viruses, usually parainfluenza virus and sometimes RSV and adenovirus. The symptoms are most severe in children of 6 months to 3 years old. However, older children are known to be infected too. Some children are more prone to developing croup when they get a viral upper respiratory infection. In most cases, the viral croup is mild and can be treated at home. Croup, rarely can be severe or even life- threatening.

At first, a child may have cold symptoms, like a stuffy or runny nose and a fever. As the upper airway (the lining of the windpipe and the voice box) becomes more inflamed and swollen, the child may become hoarse, with a harsh, barking cough. This loud cough, which is characteristic of croup, often sounds like the barking of a seal.

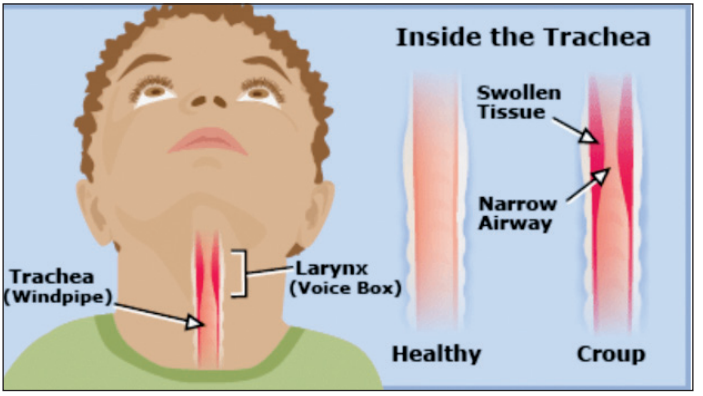

Figure 5 Croup

If the upper airway continues to swell, it becomes even more difficult for a child to breathe and a high-pitched or squeaking noise during inhalation (called stridor) is heard. A child also might breathe very fast or have retractions (when the skin between the ribs pulls in during breathing). In the most serious cases, a child may appear pale or have a bluish color around the mouth due to a lack of oxygen. Symptoms of croup are often worse at night and when children are upset or crying. Besides the effects on the upper airway, the viruses that cause croup can cause inflammation further down the airway and affect the bronchi (large breathing tubes that connect to the windpipe).Croup symptoms generally peak 2 to 3 days after the symptoms of the viral infection begin. Viral croup usually lasts 3 to 7 days.

Croup can be detected by listening for the telltale barking cough and stridor. Children with croup are often diagnosed based on the parents description of symptoms such as a fever, runny nose, and congestion, and if the child has a history of croup or upper airway problems. A neck x-ray is not routinely done, unless if the croup is severe. An X-ray of a child with croup usually will show the top

of the airway narrowing to a point, which is called, "steeple sign." Most, though not all, cases of viral croup are mild. In severe cases, hospitalization is required. Steroids and epinephrine nebulizers decrease the airway swelling. Oxygen also might be given, and sometimes a child with croup will remain in the hospital overnight for observation.

BACTERIAL PATHOGENS

Bacterial pneumonia is a type of pneumonia caused by bacterial infection. Bacterial pneumonia is more common in children living in developing countries. The reason is chronic malnutrition, overcrowding, and chronic injury to the respiratory tract epithelium from exposure to cooking and heating with biomass fuels without adequate ventilation are all rampant in developing countries.

Various tests that determine bacterial products in blood, respiratory tract secretions, and urine have been used to ascribe a causative role of bacteria but are positive in less than 10% of cases. The leading causes of bacterial pneumonia in children are caused by *S. pneumoniae, H. influenzae and S. aureus*. *S. pneumonia* is the single most common cause of pneumonia beyond the first few weeks of life. In countries where immunization with Hib vaccine is given as part of the national immunization program, including Malaysia, United States and many parts of Europe, the frequency of Hib infection, including pneumonia has markedly reduced. *S. aureus* is an infrequent cause of community-acquired pneumonia, accounting for 1-5% of cases in which a bacterial cause is identified, but it is a recognized cause of influenza-associated community acquired pneumonia. The other bacteria, especially Gram-negative organisms, are rare causes of pneumonia in previously healthy children.

Streptococcus Pneumoniae

Pneumococcal pneumoniae is a type of bacterial pneumonia that is specifically caused by *S. pneumoniae* is also called pneumococcus. Benjamin White in 1938 wrote that pneumococcus is altogether an amazing cell. Tiny in size, simple in structure, frail in make-up, it possesses physiological functions of great variety, performs biochemical feats of extraordinary intricacy and, attacking man, sets up a stormy disease so often fatal that it must be reckoned as one of the foremost causes of human death. More than 60 years later, the pneumococcus remains a major cause of respiratory and invasive diseases. The World Health Organization (WHO) estimates that 1.6 million die every year from the disease, 0.7-1.0 million of which are children aged <5[1]. *S. pneumoniae*remains the leading cause of community-acquired pneumonia among children worldwide, with the highest incidence occurring in infants less than two years old (Rec W.E, 2007).

Pneumococcal infection causes a variety of clinical syndrome. The manifestations can be broadly divided into invasive or non-invasive pneumococcal disease. Invasive pneumococcal disease refers to disease in which pneumococcal enters a normally sterile site, such as blood, cerebrospinal fluid (CSF), pleural fluid, joint fluid or pericardial fluid. Non-invasive disease includes otitis media, sinusitis and bronchitis and is generally regarded as less serious compared with invasive pneumococcal disease (Randle E, 2011).

PEDIATRIC INVASIVE PNEUMOCOCCAL DISEASE IN A TERTIARY HOSPITAL IN MALAYSIA

Introduction of pneumococcal conjugate vaccines has successfully reduced the incidence of vaccine-type invasive pneumococcal disease. The pneumococcal conjugate vaccine has been licensed

in Malaysia since March 2006. However, the vaccine has not been included as part of the routine vaccination program in Malaysia despite it being projected to prevent around 260,000 deaths annually as well as having potential to mitigate the widespread antibiotic resistance (Sinha A, 2007).

There were limited publications on pneumococcal infection in Malaysia (Lim LH, 2007, Rohani MA, 1999). Most of the published data focused on serotypes isolated and antibiotics resistance pattern. The clinical manifestations of invasive pneumococcal disease in Malaysia were examined in a retrospective study by N. Othman et al (2010). The study was conducted in Institute of Paediatrics Hospital Kuala Lumpur (IPHKL), a tertiary pediatric hospital with 500 beds which provides both primary and tertiary care. Twenty-five children (0-12 years old) were hospitalized from March 2002 till Nov 2005 for invasive pneumococcal disease, who satisfied a clinical case definition of the disease: Isolation of *S. pneumoniae* from normally sterile specimen sites from the body (e.g.: blood, cerebral spinal fluid, peritoneal fluid or joint aspiration). For this study, the diagnosis of pneumococcal pneumonia was made when the clinical manifestation of pneumonia was supported by chest x-ray evidence if available, with isolation of *S. pneumoniae* from blood or pleura fluid (pleura: lining of the lungs). Likewise meningitis (infection of the lining of the brain)/sepsis (severe blood infection that can lead to organ failure and death)/septic arthritis (infection of the joints)/peritonitis (infection of the peritoneum) is defined as clinical features consistent with the site of infection and isolation of the pathogenic organism from the respective site or blood.

The study showed that two-thirds of the patients (17/24, 66.7%) was below 2-years-old and pneumonia represented half of these cases. This was consistent with other studies worldwide that showed

the highest incidence of this infection occurs in children below two years of age (Rec W. E 2007). The study revealed sepsis and pneumonia were the commonest presentation, and this was followed by meningitis (table 2). Of the 14 patients with pneumonia, three developed pleural effusion or empyema (collection of fluid/pus in the lungs), of which only one patient required chest tube drainage. None of the patients required any form of surgical intervention.

Nine patients had co-morbid factors identified; four had hematological conditions, three related to prematurity and the remaining two were associated with nephrotic syndrome (a nonspecific disorder in which the kidneys are damaged, causing them to leak large amounts of protein from the blood into the urine). None of the patient received any types of pneumococcal vaccine before the current admission. Only three patients received antibiotics within 30 days of admission.

Table 2 Manifestations of invasive pneumococcal disease

Diagnosis	Number of patients (%)
Sepsis	14 (50)
Pneumonia	14 (50)
Meningitis	10 (41.7)
Cellulitis	3(12.5)
Peritonitis	2 (8.3)
Septic arthritis	2 (8.3)
Acute glomerulonephritis	1 (4.2)

More than half of the patients required prolonged hospitalization (stayed more than two weeks) and ventilation (duration1-24 days). Seven of these children, who were ventilated and had prolonged

hospitalization, also had pneumonia. There were two mortalities, both were infants (age less than one year) and meningitis was the cause of death. The high percentage of mortality (8.3%) and patients requiring intensive (54.2%) support could be explained by the study centre being a tertiary referral centre which provides support for referral cases from the whole country. The mortality data presented concurs with other studies on invasive pneumococcal disease in other regions of the world, ranging from 3.2% to 23.5% and meningitis is the cause of fatality in most of the studies (Bravo L., 2009, Katherine L O' Brien, 2009).

In our study, atypical presentations of invasive pneumococcal disease were encountered. Three patients, all premature newborns had invasive pneumococcal disease within the first 24 hours of life and all survived. They presented with manifestations of meningitis, pneumonia and pneumonia with sepsis respectively. From literature search, *S. pneumoniae* is a rare cause of invasive pneumococcal disease in newborns (Westh H, L Skibsted et al. 1990; Geelan S.L, 1990). *S. pneumoniae* is not a normal vaginal flora. The newborns acquire the infection through maternal bacteremia (*S. pneumoniae* in blood), transplacental, ascending infection from genital tracts, while passing through birth channel or through the respiratory tract at postpartum period. The clinical course strongly resembles early onset group B streptococcal disease. However, in comparison with group B streptococcal, it has higher mortality and morbidity. In view of the high invasion rate and potential disastrous outcome, treatment of the asymptomatic newborns colonized by *S. pneumoniae* has been recommended.

The second atypical presentation reported in our series was a healthy infant presenting as purpura fulminans (I. h. Intan, 2009). The majority of cases of purpura fulminans are associated with *Neisseria meningitidis* sepsis (Purpura fulminans: a rare

life threatening skin disorder with extensive areas of blueblack hemorrhagic necrosis associated with sepsis or serious infection). However, other bacteria, including *S. pneumoniae*, can also be the cause and in most cases it occurs in asplenic (condition without a spleen) or immunocompromised adults rather than in children. To our knowledge, only five cases of pneumococcal purpura fulminans in healthy children have previously been reported (Noguera A, 2004).The mortality rate in this condition has recently been significantly reduced, largely because of aggressive replacement of platelets and coagulation factors.

Post-infectious acute glomerulonephritis (AGN) is a common disease in children and classically caused by nephritogenic strain of group A *B*-hemolytic *Streptococcus (GABHS)*.Affected children with AGN present with red urine described as smoky coca-cola like colour (hematuria), puffy eyelids in the morning and may progress to swelling of both limbs. Most of the time the swelling is not marked and associated with reduced urine output and hypertension. Glomerulonephritis following infections with other microbial agents, such as *S.pneumoniae* has rarely been described. To date 8 cases have been reported over the past 3-4 decades; 5 in children and 3 in adults (Chanceller Lech A, 2010, Phillips J, 2005). In these reported cases, pneumococcal serotypes 5, 6B, 7, 9, 14, 15 and17F have been described as nephritogenic strains. Similar to our case, almost all reported cases have reported pneumococcal bacteremia suggesting that the rarity of pneumococcal glomerulonephritis could be attributed to the invasive form of pneumococcal infection itself. Our patient had an uneventful acute nephritis and a stable blood pressure throughout hospitalization (Intan HI, 2007).

EMERGENCE OF PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* (PRSP)

A case of a 19-month old with PRSP with severe pneumonia and bilateral pleural effusion, prompted us to embark on a literature search on this growing problem (MZA Hamid et al, 2008).

Although *S. pneumoniae* was once considered to be routinely susceptible to penicillin, resistance started to develop in the 1960s. Penicillin kills the bacteria by binding to the protein on the cell wall and reducing the peptide chain production, which further weakens the cell wall. Minimal inhibitory concentration (MIC) is a scale that measures the resistance of the bacteria to a particular antibiotic. Resistant strains are categorized into susceptible if MIC is less than 0.06 ug/ml, of intermediate if MIC is 0.1 t0 1.0 ug/ml and resistant if MIC is greater than 2.0 ug/ml.

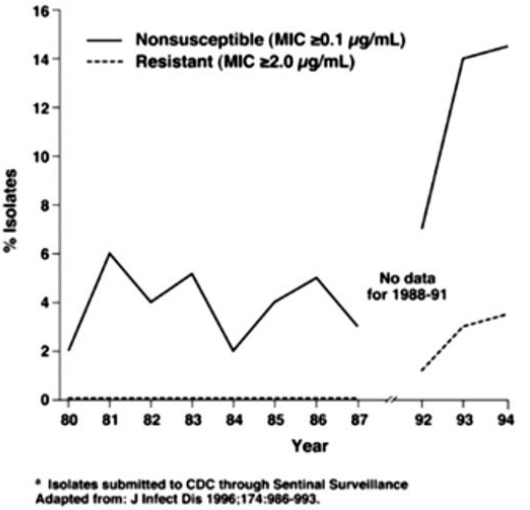

Figure 6 Prevalence of Penicillin Nonsusceptible and Resistant Isolates of *S. pneumoniae*

Heathet PT et al (2002) found that the prevalence across Europe in a decreasing order was as follows: Spain (51.0%) followed by Hungary (57.8%), and lowest in more developed countries namely Germany (1%) and Netherlands (2%). Prevalence was also noted to be significantly higher in other parts of the world, such as in South Africa which reported 62.2% cases of penicillin-resistant community-acquired pneumonia and approximately 70% in population studied in South Korea. The Asian Network for Surveillance of Resistant Pathogens (ANSORP) documented that in Malaysia there was an increase in incidence of nearly four-folds (10% in 1996 and 43% in 2003) of penicillin –resistant pneumococcal pneumonia, however the cases reported in our country might represent only the small fractions of the actual problem (Song JH, 2004).

Identifiable risk factors associated with PRSP include previous use of antibiotics, children from countries with high prevalence of antibiotic resistance, patients on private medical coverage, immunodeficiency patients and those not responding to conventional antibiotic therapy (Deeks SL, 1999).

Due to the complexity of the PRSP, it leads to believe that any pneumococcal pneumonia warrants alternative and most of the time expensive antibiotics. However evidences have suggested penicillin or earlier generation cephalosporin group antibiotics appeared to be adequate in treating susceptible or intermediate resistant SP. Clinicians should reserve the use of third-generation cephalosporin and to certain extent vancomycin, only to the cases suspected to be pneumococcal resistance (MIC > 2.0 μg/ml) (Heath PT). It also showed that PRSP were no less virulent when compared to other normally susceptible strains. Mortality rate due to PRSP strains and non-PRSP strains showed no significant difference as reported by Deeks et al (1999).

The emergence of these PRSP strains has made the management of these cases more difficult. This highlights the importance of possible prevention by vaccination coverage in these vulnerable children. Nonetheless, at present it is imperative for all clinicians to be aware of PRSP pneumonia and how best to identify and manage it effectively.

Staphylococcus aureus

Staphylococcus was first identified in Aberdeen, Scotland (1880) by the surgeon Sir Alexander Ogston from a surgical abscess in a knee joint. This name was later appended *to S. aureus* by Rosenbach who was credited by the official system of nomenclature at the time. It is estimated that 20% of the human population are long-term carriers of *S. aureus*, which can be found as part of the normal skin flora and in anterior nares of the nasal passages. *S. aureus* is a successful pathogen due to a combination of nasal carriage and its bacterial immuno-evasive strategies (Sarah S. Long, 1997)

Most of the time, the organism does not cause any harm; however, sometimes it causes infections including pneumonia. Until recently, staphylococcal pneumonia was considered an uncommon community-acquired pneumonia, accounting for 1%–5% of all community-acquired pneumonia cases and occurring primarily in patients with influenza. In addition, *S. aureus* was recognized as an important but infrequent cause of nosocomial pneumonia. However, in the past 2 decades, there have been important changes in *S. aureus* pulmonary infection. First, methicillin-resistant *S.aureus* (MRSA) emerged as a nosocomial pathogen in the early 1960's, soon after the introduction of methicillin. Since then, it has become the main cause of nosocomial infections. It is now present in the hospitals of most countries (Ayliffe G, 1997; Wenze RP 1991). All MRSA strains were once susceptible to vancomycin.

However, reduced susceptibility to MRSA to vancomycin, known as vancomycin -intermediate *S.aureus* (VISA) was first identified in Japan in1996 and has since been found in hospitals elsewhere in Asia as well as other parts of the world (Appelbaum PC,2007). These bacterial strains present a thickening of the cell wall, which is believed to reduce the ability of vancomycin to diffuse into the division septum of the cell required for effective vancomycin treatment. In 2002, the strain became completely resistant to vancomycin; labeled as vancomycin-resistant *S.aureus* (VRSA). It was isolated from the catheter tip of a diabetic, renal dialysis patient in Michigan. From 2002 to 2010, ten additional VRSA isolates were reported, eight from the United States, one from Iran, and one from India. The appearance of these strains make treatment of infected patients much more difficult, especially in situations where an effective treatment for an infection is needed urgently, before detailed resistance profiles can be obtained.

Until recently, most of the MRSA strains causing health care–associated pneumonia (HAP), were labeled hospital-acquired MRSA and contained the staphylococcal cassette chromosome (SCC) *mec* types I–III (Kaplan SL, 2005). Recently, however, a new variant of MRSA has emerged as a pulmonary pathogen. This new variant of *S. aureus* that causes pneumonia is community-acquired MRSA (CA-MRSA), containing SCC*mec* type IV-V. Table 3 differentiates health-care associated MRSA from community associated MRSA.

Table 3 Comparison of CA-MRSA and HA-MRSA

Characteristics	CA-MRSA	HA-MRSA
Clinical spectrum	Skin and soft tissue infections	Respiratory tract infections Urinary tract infections Bloodstream infections Others
Epidemiology	Clusters and outbreaks in 'closed populations' such as jail inmates, nurseries, drug users sharing same needles Multiple clonal origins	Outbreaks healthcare-associated Dissemination of a few clones
Underlying condition	Dermatological	Healthcare-associated risk factors
Age group	Younger	Older
Resistance pattern	Susceptible to multiple antibiotics	Resistant to multiple antibiotics
Genotypic characteristics	Mainly SCC*mec* type IV and V, PVL present	Mainly SCC*mec* type I, II and III PVL absent

Nasal carriage of *Staphylococcus aureus* Among Healthy Adults

In humans, *S. aureus* colonization is mainly found in the anterior nares (Lowy FD, 1998). Nasal carriage of *S. aureus* is a potential source of infection and colonization often precedes infection. In general, nasal carrier rates among hospital personnel and patients (60-70%) are much higher as compared to those among community carriers (30-50%).Data on the carriage rate and antibiotic sensitivity pattern of *S.aureus* strains prevalent in the community are not available for many developing countries including Malaysia. Furthermore, most studies on nasal carriers on *S.aureus* in Malaysia were carried out in hospital and outpatient settings, involving patients and hospital staff.

We conducted a cross-sectional study involving 346 healthy adults over 18 years of age. They were both preclinical and health sciences students, staff, and visitors at the preclinical block of the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. Individuals who were recently hospitalized were excluded and most stayed on campus. Nasal swabs were examined for the presence of *S. aureus*. Epidemiological information concerning risk factors for nasal carriage was also obtained. Antibiotic susceptibility testing was performed using the disk diffusion method according to the National Committee for Clinical Laboratory Standards guidelines. MRSA strains isolated were further subjected to pulse-field gel electrophoresis analysis.

The study showed a prevalence rate of 23.4% (81/346) of *S. aureus* nasal carriage in the study sampled. From 346 nasal swabs collected, only 1 MRSA isolate was identified while 80 persons were found to be nasal carriers for *methicillin sensitive S. aureus* (MSSA). The MRSA strain (different from the hospital strain) was isolated from a healthy individual who had noprevious history of

hospitalization and antibiotic intake prior to the sampling. However, history of contact with hospitalized persons was not available. In this study, the low prevalence of MRSA nasal carriage in a healthy population appears to contrast with the diverse dissemination of methicillin-sensitive *S. aureus* (MSSA). MRSA strains are known to exhibit lower adherence to the nasal mucosa, rendering isolation of these strains from colonized nares seemingly more difficult.

Consistent with previous reports, we found that smoking, particularly among ex-smokers, was associated with *S. aureus* colonization. Smoking is known to alter the respiratory mucosal surface, facilitating the binding of potential pathogens, particularly *S.pneumoniae*and *H. influenzae*, and to a lesser extent *S. aureus*. This leads to an increased risk of airway colonization and development of pneumonia (El Ahmer OR, 1999). Raman et al also found that pneumococcal adherence in some ex-smokers remained high for up to 3 years after smoking cessation (Raman AS, 1983). However, the etiological basis of this observation is unknown. Our data also indicated that oral contraceptive users are at increased risk of harboring *S. aureus* nasal carriage. As there is a scarcity of data on this specific interaction, further studies are required to determine the actual relationship of oral contraceptives to *S. aureus* nasal carriage. We first reported the appearance of CA-MRSA in Malaysia and concluded that MRSA nasal colonization was found to be low outside of the health care environment. Smokers and oral contraceptive users have high nasal carrier rates.

Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nosocomial Infection in Malaysia

As there was an unusual increase in the number nosocomial cases during the surveillance audit in Institute Pediatrics, Hospital Kuala Lumpur in 1998, we studied retrospectively the prevalence of

MRSA nosocomial infection in the pediatric wards (Norlijah O, 2004). In our study, we also identified the susceptible groups of patients, ascertain the associated risk factors and further determine the antibiotic susceptibility pattern of MRSA isolates of these patients during a six-month period study in that year. The definition of nosocomial infection followed the Center of Disease Control (CDC) criteria; is defined as those infections that occur or originate in a hospital or hospital-like setting. In our study it was considered a nosocomial infection if positive MRSA culture was obtained from specimens and appropriate therapy instituted and deemed as an infection by the physician in-charge. Colonization was excluded.

The nosocomial rate was found as 0.93% (206/20893); MRSA was second to *Escherichia coli*. A total of 25 cases had MRSA infection, with a median age of 36 months, ranging between day 4 of life to 14 years of age. Figure 7 illustrates the distribution of MRSA nosocomial infection in the respective wards; the neonatal ward had the highest number of cases as compared to the other areas in the hospital.

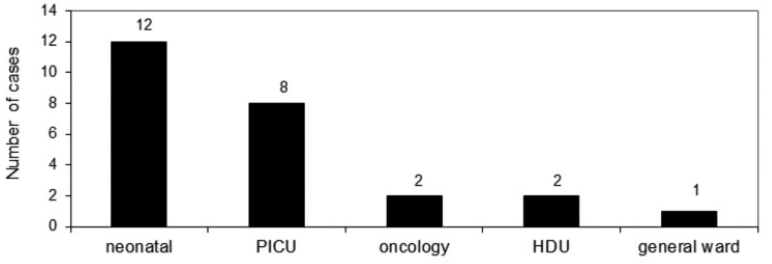

Figure 7 Number of cases of MRSA nosocomial infection in the respective wards

The neonates are most susceptible as their immunity has hardly developed, have more complications, exposed to various modalities of invasive therapies and tend to stay in the hospital longer (Val G Hemming, 1970). There were two distinct groups identified; those aged less than 3 months and those aged 3 months and older. Pneumonia was the presenting feature in the older age group while the younger ones manifested as septicemia. None of the patients presented with urinary tract infection or meningitis. Diagnosis of any form of meningitis is important, as prognosis is dismal and associated with high mortality. Lumbar puncture could not be obtained as permission was not granted from parents/guardians in most cases and occasionally patients were too ill to be subjected to the procedure.

We also found that more than one predisposing factor was present in each case of infection, as shown in Table 4. Prolonged hospitalization and co-morbid conditions were predominantly associated with increased MRSA nosomial infection in the older group. All isolates were sensitive to vancomycin, fusidic acid and rifampicin, and resistant to erythromycin and tetracycline. A high percentage of the isolates were resistant to sulphamethoxazole-trimethoprim (88%), chloramphenicol (80%), gentamacin (64%) and amikacin (50%). One isolate was resistant to ciprofloxacin. Vancomycin was the antibiotic of choice while a combination of fusidic acid with rifampicin was administered to one patient.

Table 4 Predisposing factors associated with nosocomial MRSA infection

No of patients	Prolonged hospitalization	Therapy induced	Post-surgical	Intravascular catheters	Ventilation	Others
6 preterm babies	5	2 prolonged antibiotics	1	3	2	3 TPN
6 term babies	1	1 prolonged antibiotics	None	6 (All)	6 (All)	2 TPN/ Dextrose 15% 1 peritoneal dialysis 1 exfoliating skin 1 multiple chest tube drainage
6 older aged group	13 (All)	3 cytotoxic 6 prolonged antibiotics 4 steroids	6	None	2	4 immunocompromised disease

To conclude, it should be stressed that MRSA prevention and control should consist of isolation of patients with MRSA especially in intensive-care units, strict enforcement of hand-washing and other aseptic techniques, use of disposable equipment and products, and continuing education of medical personnel on the communicability of MRSA (Mulligan M ,1993). Early identification of patients at risk, prompt discharge of patients, and preventing dissemination while performing invasive procedures achieve reduction of MRSA infection/colonization in the hospital.

Predominance and Emergence of Clones of Hospital-Acquired Methicillin-Resistant *Staphylococcusaureus* in Malaysia

As mentioned earlier, MRSA causes both health care-associated (HA) and community-acquired (CA) infections. Modern MRSA has evolved from several successful clonal lineages of methicillin-susceptible *S. aureus* strains via acquisition of a mobile genetic element called staphylococcal cassette chromosome *mec*(SCC*mec*). This element contains the *mecA*gene, which encodes penicillin-binding protein 2 (PBP2) with significantly reduced affinity for B-lactams (Robinson, D, 2003)

Increased emergence of multidrug resistance among MRSA strains has become a major concern in the hospital environment, as it invokes a tremendous financial burden and enhanced morbidity and mortality due to hard-to-treat systemic infections. MRSA was introduced into Malaysia in the early 1970s , (Lim, V. K 1987), and a review of the records of the microbiology laboratories of all state hospitals in Malaysia showed that the proportion of MRSA isolates from *S. aureus*-infected individuals had been approximately 21% throughout the last few years.

Phenotypic MRSA typing methods are not suited for detailed epidemiological surveillance; in tracing the nosocomial sources and transmission routes of the bacterial pathogen. Several superior molecular typing methods can be used for supporting infection control and these include:

- Pulsed-field gel electrophoresis- the current gold standard method
- Multilocus sequence typing (MLST) -has recently been proven to be the best for long term global epidemiological and bacterial population genetics studies
- Spa typing: Similar sequence typing (a combination of alleles from the seven loci forms a sequence type) are grouped into clonal complexes
- Virulence gene profiling

Molecular typing data on HA MRSA isolates in Malaysia are sparse in comparison with those on strains deriving from Europe, the United States, or Japan. Pilot data hinted at the predominance of a single MRSA genotype in Malaysia. This is similar to the situation in many other Asian countries (Ko, K. S. 2005; Nor Shamsudin, M. 2008)

Hospital Kuala Lumpur (HKL) is the largest government tertiary referral hospital with 81 wards and 2502 beds. Each year at least 1 million people (3.8% of the total Malaysian population) are referred and treated here from all states in Malaysia. The epidemiology of any nosocomial infection in this hospital will most likely reflect the nation's epidemiology as it is a major referral hospital. It also records an annual MRSA prevalence of over 40%. Many of these MRSA strains are multidrug resistant. As additional epidemiological studies were clearly warranted in order to increase

the insight into the dynamics of MRSA epidemiology in Malaysia, it prompted us to embark on a study to characterize the current Malaysian MRSA isolates and further determine their molecular epidemiology by molecular methods as described above.

The clinical isolates collected were from October 2007 to September 2008. Out of a total number of 1,887 MRSA strains, a random selection of 389 strains was investigated in molecular detail. All isolates previously identified to the species labelled bythe hospital laboratory were reconfirmed in the microbiology laboratory at Universiti Putra Malaysia by standard methods such as Gram staining, catalase testing, tube coagulation, mannitol testing, and MRSA screen latex agglutination testing (Denka Seiken Co., Ltd., Tokyo, Japan). Isolates were confirmed as MRSA by oxacillin and cefoxitin susceptibility testing according to the CLSI guidelines. All isolates were also reevaluated for the presence of the *mecA*gene by PCR. Confirmed MRSA isolates were then stored at _80°C in Luria-Bertani broth supplemented with 20% glycerol and subsequently subjected to pulse-field electrophoresis, MLST, spa typing and virulence gene profiling

The majority affected were adults. The median age of patients in the study was 47.8years, and the age range was from 4 days to 88 years. In agreement with earlier reports, the prevalence of MRSA in this study did not vary by gender (Kairam, 2009). When data were stratified according to the three major ethnic groups in Malaysia, the prevalence of MRSA infection among Indians was found to be significantly elevated. A similar observation was reported for CA MRSA in African-American children (Sattler, C. A, 2002).

The highest rate of MRSA, as reported from our general medicine ward, is in the dermatology ward, with a high rate of skin and soft-tissue infection. The short hospital stay and adequate antibiotic therapy in otherwise healthy patients in the maternity

ward explain the low prevalence in that ward (Udo E. E, 2006). The frequencies of MRSA isolates obtained from different type of specimens are summarized in Figure 8. Respiratory samples were second to purulent specimen from skin and soft tissues; this finding is expected as these are common commensal sites for this organism.

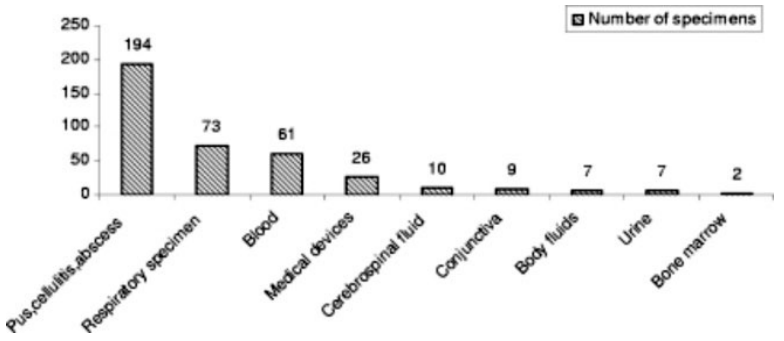

Figure 8 Number of specimen from several sites completed positive for MRSA

Several international epidemiological investigations demonstrated that most hospital-acquired MRSA infections are caused by a relatively small number of epidemic MRSA clones spread worldwide. The most frequently encountered clones are the Iberian (ST-247-IA), Brazilian/Hungarian (ST-239-III), Berlin (ST-45-IV), New York/Japan (ST-5-II), pediatric (ST-5-IV), EMRSA-15 (ST-22-IV), and EMRSA-16 (ST-36-II) clones (33). We here showed the predominant clone in Malaysia was ST-239 (CC8), *spa* type t037, and possessed SCC*mec* type III/IIIA . This clone is also dominant in most other Asian countries except South Korea and Japan (Ko, K. S, 2005).

We present the first cases of infection by ST-22, SCC*mec* type IVh, with three different *spa* types (t932, t3213, and t4184)

in Asia. These strains were mainly isolated from blood (66.6%) or skin and soft-tissue infection (33.3%). SCC*mec*IVh, present in a recently described specific subtype ofEMRSA-15 (ST-22), was reported for the first time in Portugalbut shortly after from places as distant as Sweden (Berglund, C., 2009) and lately from Spain (Vindel, A., 2009).The SCC*mec*IV element is small in comparison to elements such as SCC*mec* type III; the small size enables easier spread among *S. aureus* strains. As a possible consequence of its enhanced mobility, it is also more variable than other SCC*mec* types. The detection of ST-22(which is one of the predominant MRSA clones in Europe, Australia, New Zealand, in Singapore and later in Malaysia) strengthens the case for the epidemic nature of this clone and also suggests that it may easily spread to other Southeast Asian countries.

A limited number of community-acquired MRSA strains were also detected. These included ST-188/t189 (2.1%), ST-1/t127 (2.3%), and ST-7/t091 (1%). Panton-Valentinleukocidin (PVL) was detected in all ST-1 and ST-188 strains. The majority of the isolates carried *agr* I, except that ST-1 strains were *agr*III positive.

The results revealed the predominance of ST-239-SCC*mec* III/IIIA and the penetration of ST-22 with different virulence gene profiles. In addition, minor groups of community-acquired MRSA strains detected in the current study indicate the abilityof such strains to settle in the hospital environment. The emergence in Malaysia of novel clones of known epidemic and pathogenic potential should be taken seriously.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a very small bacterium in the class Mollicutes. *M pneumoniae* is the smallest free-living organism capable of self-replication smaller than some viruses; it causes

the disease mycoplasma pneumonia, a form of atypical bacterial pneumonia. This species lacks a cell wall, like all Mollicutes. Instead, it has a cell membrane that incorporates sterol compounds, similar to eukaryotic cells. It obtains these sterols from the host serum, allowing it to retain a simple structure. Lacking a cell wall, these organisms are resistant to the effects of penicillins and other beta-lactam antibiotics, which act by disrupting the bacterial cell wall (Jawetz, 1995).

In 1938, Reimann described the first cases of mycoplasmal pneumonia in man and coined the term "primary atypical pneumonia" after observing 7 patients in Philadelphia with marked constitutional symptoms, involving the respiratory tract, and runs a protracted course with gradual resolution. Peterson discovered the phenomenon of cold agglutinin in 1943; high titers of cold agglutinins in patients with primary atypical pneumonia were discovered accidentally. In 1944, Eaton was credited with discovering a specific agent, coined Eaton's agent, as the principal cause of primary atypical pneumonia.First thought to be a virus, Eaton's agent was proved to be a *Mycoplasma* species in 1961.

M. pneumoniae is a common cause of community-acquired pneumonia. It can cause upper or lower respiratory infections, or both. *M.pneumoniae*was first isolated in cattle with pleuropneumonia in 1898. Once considered to occur primarily among adolescents and young adults, *M. pneumoniae* is increasingly recognized as a cause of lower respiratory tract disease in young children.

Although LRIs due to *M. pneumoniae* classically result in mild and self-limited disease, more severe illness is known to occur as illustrated in our case of a 5-year-old boy who presented with a short history of fever, cough and respiratory distress (N Othman, 2005). During this episode, the patient sought treatment from a general practitioner twice and was prescribed antipyretic

and antibiotics but the illness did not improve. His chest X-ray revealed large right pleural effusion compatible with the clinical findings on examination. An immediate chest drainage was inserted and purulent discharge with large amount of pus cells were shown microscopically. The diagnosis of *M. pneumoniae* infection in this case was made on clinical and serologic grounds as serologically there was a four –fold rise in *M. pneumoniae*IgMtitre (a single initial titre of 1:5120 followed by four-fold rise in antibody titre to 1:>20,480). The fever took 15 days to settle. The empyema required drainage for more than 2 weeks and the infection resolved with a course of six weeks of antibiotics. This case highlights the importance of considering *M. pneumoniae* infection as a cause of community-acquired pneumonia especially in children over 5-years old, of whatever the severity may be, and of starting the appropriate antibiotic therapy.

M. pneumoniae infection was also previously thought to cause only benign respiratory disease affecting the upper respiratory tract more than lower. Further reports showed it could also cause severe disease not limited to the respiratory tract. Abnormalities in almost every organ system have been associated with *M. pneumoniae* infection including neurologic, dermatologic, gastrointestinal, hematologic, cardiovascular, musculoskeletal and renal.

Clinical detection of *M. pneumonia*e is problematic given both the absence of any distinctive presenting clinical manifestations, routine laboratory parameters, or radiographic findings and lack of standardized, rapid diagnostic test. Serologic testing is commonly used to diagnose *M. pneumoniae* but is not useful for acute management because a convalescent serum is required. Culture is time consuming and expensive, while polymerase chain reaction, although potentially allowing a rapid diagnosis, is costly and neither culture nor PCR are available in most centres (Honda J, 2000).

Mycoplasma pneumoniae Infections in Australian Children

The clinical features of *M. pneumoniae* are well elucidated in other continents such as America, Europe and Asia. As there was no data on *M.pneumoniae* infections in Australia then, the clinical features in children were examined in a restrospective study by N Othman et al (2005). We observed 76 children, who were either seen as out-patients or hospitalized from June 1997 to August 2002. The included cases satisfied a case definition of *M. pneumonia*e: a serological diagnosis of a four-fold rise in complement fixation titre (CFT) or a single CFT of 1:64 or greater, associated with clinical manifestations compatible with *M. pneumoniae* infection.

There were 42 (55.3%) boys and34 (44.7%) girls. The age distribution is shown in Figure 9. The incidence of *M. pneumoniae* pneumonia was still the highest, nevertheless, among the schoolchildren aged 5–9 years, with a second peak in children 1–5 years of age. Infants were not completely spared from infection, but we found, like others, that infants less than 1 year old were rarely affected. *M.pneumoniae* pneumonia was traditionally thought to occur mainly in school-aged children and to be rare in children under 5 years of age. However, from the 1970s onwards, studies indicated *that M. pneumonia*e infection was not rare in children less than 5 years old (Ponka A, 1983; Bosnak M, 2002). Our results are consistent with other studies, which emphasized that *M. pneumoniae* should be kept in mind as a cause of community-acquired pneumonia in children less than 5-years-old.

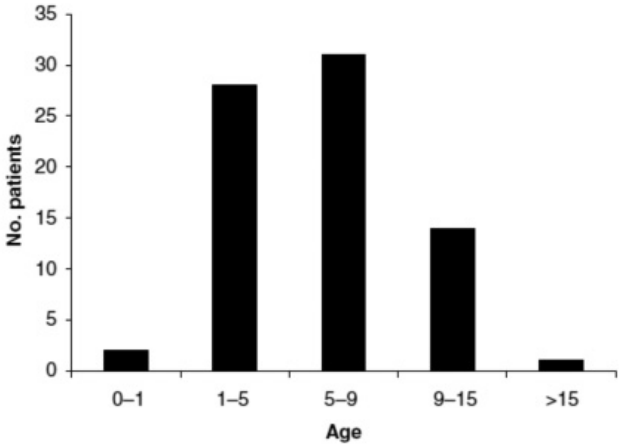

Figure 9 Age distribution of patients admitted with *Mycoplasma pneumoniae*infection.

This infection was found to occur throughout the year, with 4-6 cases seen in most months as seen in other continents as Europe and America. A peak was observed from June to July with a slightly less than a third (23/76,30.1%) of the total cases were seen during that period of the year.

The clinical picture observed in our study, did not differ greatly from those described in other studies (Clyde AW, 1993; Cherry JD, 2004). Fifteen children had extra respiratory manifestations, majority (11/76, 0.14%) presented with rash, of which two had erythema multiforme (skin disorder : may be severe and has classical "target lesionappearance, with a pink-red ring around a pale center)and Kawasaki respectively (autoimmune disease affecting the medium-sized blood vessels throughout the body become inflamed, untreated leads to coronary artery aneurysm).

Comparing children infected with *M.pneumoniae*over 5 years old versus ≤5yearsdemonstrates that the younger children were

more likely to have coryza,diarrhoea, vomiting, rapid breathing and recession.

The proportion of younger children to be hospitalized was also slightly more than the older children. Five patients had mixed viral/bacterial infections in this series. In contrast to a previous large study, co-infections of *M. pneumoniae* with other organisms were verycommon, but did not appear to be associated with more severe manifestations. On laboratory assessment, the presence of thrombocytosis (defined as platelet count of more than 400 x 10^{9}/L) in 40% of the cases has not previously been reported in children. Chest-x-ray findings were none-specific. All patients were discharged alive with no sequelae except the child with meningo-encephalitis (brain infection).

In conclusion, our data underlines the role of *M. pneumoniae* in children with community-acquired pneumonia, even in children aged less than 5 years old. We found that children under 5 years old were more likely to present with non-respiratory symptoms such as diarrhea and vomiting, as well as with coryza and recession and they were as expected more likely to be hospitalized as compared to the older children.

Seropositive versus Seronegative Children with *Mycoplasma pneumoniae* Infection in Children-Could We Predict the Infection in Terms of the Clinical Parameters?

Distinguishing acute *M.pneumoniae* infection has clinical relevancebecause rapid diagnostic tools are not readily available and, more importantly, *M. pneumoniae* does not respond to the usual first-line antibiotics. The decision to commence macrolide therapy for mycoplasma infection is based on in vitro sensitivity of the organism, but this test is not available in most centers. The present

study attempts to predict *M. pneumoniae* infection in children in terms of the clinical parameters (clinical features, laboratory, and chest-x-ray findings) by comparing those with positive versus negative serology results (Norlijah Othman, 2008). We assumed that seropositive children had true *M. pneumoniae* infection and that seronegative children were not infected. Because the majority of patients had a single titer without convalescent serum available and molecular diagnostic test such as PCR of sputum was not performed for any patients, those in the seropositive group may not represent a definite infection and vice versa. Nonetheless, a seronegative group of symptomatic children is a more realistic control group than asymptomatic patients.

The diagnosis of *M. pneumoniae* infection was based on serological evidence obtained by a complement fixation test. A single antibody titre of 64 or more or a four-fold or greater rise in antibody titre between acute and convalescent serum taken 1 to 2 weeks apart was considered seropositive for *M. pneumoniae* infection. On the other hand, a patient with an antibody titre of less than 64 or with paired sera showing less than a four-fold rise in titre was considered seronegative.

A total of 151 children were included for analysis in this retrospective study. Seventy-six children were seropositive for M. *pneumoniae* and the remaining 75 were seronegative. Children with positive *M. pneumoniae* serology were slightly younger (mean age 6.3 ± 3.5 versus 6.6 ± 4.0 years) and males were slightly over-presented in both groups. The mean temperature on admission was almost identical in both groups: 37.8º C versus 37.7ºC in seropositive and seronegative patients respectively. There was no difference in either group of patients in terms of underlying diseases and positive history of cough among family members. The study showed that children infected with *M. pneumoniae* presenting with

pneumonia were more likely to have a history of fever >6 days duration, as shown in Table 5. Similarly, other studies reported that patients with *M. pneumoniae* pneumonia had a longer duration of fever compared to those without the infection (Fischer JE, 2002; Chan P, 2001). Asking a simple question regarding the duration of fever can identify patients with a higher risk of *M. pneumoniae* infection.

Table 5 Distinguishing clinical parameters between seropositive versus seronegative Mycoplasma group

	***M.pneumoniae* seropositive**		***M.pneumoniae* seronegative**		***P***
	n=76	**%**	**n=75**	**%**	
Age > 3 years	59	77.6	63	84	0.321
Family members with cough	15	17.1	6	8	0.230
Duration of fever >6 days	37	69.8	16	30.2	0.0004*
Fever	63	82.9	53	72.6	0.130
Cough	70	92.1	67	89.3	0.557
Running nose	26	34.2	30	40.5	0.423
Wheeze	27	35.5	35	46.6	0.164
Headache	9	11.8	9	12.0	0.976
Crackles	55	73.3	41	54.7	0.0172*
Bronchial breathing	7	9.3	4	5.3	0.347
Pneumonia[#]	64	84.2	36	48.0	<0.0001*

Asthma[#]	9	11.8	22	29.3	0.0078*
Upper respiratory tract infection[#]	1	1.3	9	12.0	0.0083*
Hemoglobin <10 g/L	5	7.1	1	1.5	0.102
Thrombocytosis >400 x 10^9/L	29	41.4	15	23.1	0.023*
Consolidation	56[◊]	80	35[¥]	57.3	0.0001*
Peribronchial thickening	20[◊]	37.7	33[¥]	54.1	0.0024*

**P< 0.05*

[#] Final diagnosis on discharge

[◊]M. pneumoniae seropositive n= 70

[¥] M. pneumoniaeseronegative n= 61

Seropositive children were also significantly more likely to have a discharge diagnosis of pneumonia than seronegative children while seronegative children were more likely to have a diagnosis of upper respiratory tract infection. Although most infections with *M. pneumoniae* are related to upper respiratory tract infection, and pneumonia develops in only 3% of infected persons (Clyde AW, 1993), the present study showed that *M. pneumoniae* infection was more likely to be established in cases diagnosed as pneumonia. In contrast, upper respiratory tract infection was more likely to be associated with the seronegative group. These findings supported the fact that upper respiratory tract infection is attributed to viruses more frequently than *M. pneumoniae* infection. Furthermore, it highlights that *M. pneumoniae* plays an important role in community-acquired pneumonia in children.

In terms of symptoms, no difference was found in the proportion of patients who had fever, cough, wheezing, headache,

breathlessness or coryzal symptoms although there was a trend for seropositive children to report lethargy. Crackles on physical examination were found by us to be more likely in *M. pneumoniae* pneumonia, although no specific clinical features were identified in previous studies in children (Fischer JE, 2002; Chan PW, 2001).

Chest films are useful diagnostic tools for the detection of pneumonia in children. The present study suggested that consolidation was associated with *M. pneumoniae* pneumonia, while peribronchial thickening was more prevalent in those without *M. pneumoniae* infection. Attempts to differentiate the type of pneumonia from 'characteristic' radiographic changes are likely to be unsuccessful because radiological interpretation is subject to inter- and intra-observer variability (Davies HD, 1996).

As a conclusion, identifying children with *M. pneumoniae* infection is not always easy. The differences observed between the present seropositive and seronegative children showed that there were real differences between the groups as a whole.The present study indicates that serology for *M. pneumoniae*is more likely to be positive in children with pneumonia rather than in upper respiratory tract infection. In addition, duration of fever of more than 6 days, finding of crackles on auscultation and radiographic lung consolidation are more likely to be found in *M. pneumoniae* infection. These clinical parameters should be considered when deciding if antibiotics are needed and if so whether a macrolide, the appropriate therapy for Mycoplasma infection is indicated.

VIRAL PATHOGENS

Viruses are the most common cause of lower respiratory tract disease in infants and young children, and are a major public health problem in this age group. Viral infection of the lower respiratory

tract most often is benign; however occasionally it can be fatal. Each year approximately 3% of all children less than 1 year of age need to be admitted to the hospital with moderate or severe viral lower respiratory tract infection. Costs attributable to viral lower respiratory tract infections in both outpatient and inpatient settings are an important burden on national healthcare budgets.

For optimum treatment is given at the onset of the disease, it is also important to differentiate viral and bacterial infection so that optimum treatment is given at the onset of the disease. It is also important that no antibiotics be prescribed if it is a viral infection to prevent resistance of antibiotics by the organism. To achieve this, a rapid identification of viral infection is important. This will reduce overall reduction of antibiotics use, the need of other diagnostic tests can be reduced and isolation of infected patients and subsequently help control any infection during hospital stay or nosocomial transmission (1).

There two types of LRI viruses:

A. Well established viruses
B. Newly discovered viruses / unknowns

a) Well-Established Viruses

These are known to cause seasonal infections. Up until two decades ago only influenza, respiratory syncythial virus (RSV), parainfluenza virus, rhinoviruses, enterovirus and adenovirus were the established causes.

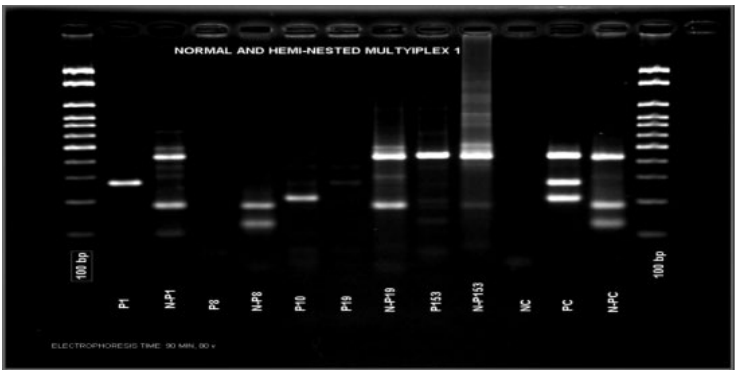

Figure 10a Multiplex PCR for detection of respiratory infections

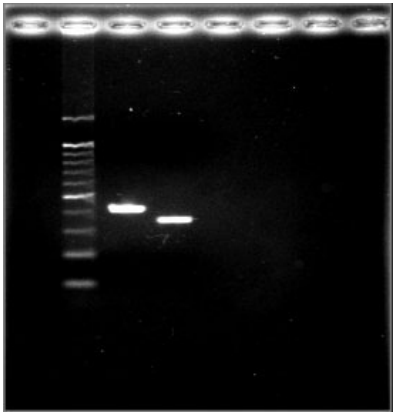

Figure 10b Detection of HBOV using PCR

A summary of the common diseases and seasonal outbreaks of LRI of these viral pathogens is given in the following Table 6.

Table 6 Summary of diseases caused by established viruses

Etiological agent	Disease	Seasonal remark
Influenza virus A and B (H3N2)	Viral syndrome : Predominant fever and respiratory syndrome Bronchitis and pneumonia in young infants, occasionally myocarditis, more severe disease with cardiac and neuromuscular disorder.	Winter months ; viral syndrome Most severe in young group (infants & young children)
RSV	Bronchitis & pneumonia lower respiratory disease children less 12 years Most common cause of LRI (Woensel)	Seasonal ; peak –Jan to March Children with a history of premature or under lying cardiac respiratory disorder suffer severe course
Parainfluenza virus type 1 to 4 (4a &4b)	Tend to cause upper respiratory tract symptoms Especially coup 15% bronchitis and pneumonia	Late fall

Rhinovirus	Traditionally caused URTI; recently pneumonia and next most important cause of bronchiolitis. Established role in exacerbation of asthma and chronic obstructive airway disease	All year round Infection with one serotype leads to lifelong immunity
Enterovirus (Especially Echovirus and Coxsackie)	Severe pneumonia caused by Echovirus, especially in infants Coxsackie predominantly URTI Bronchiolitis uncommon agent Hemorrhagic conjunctivitis (Enterovirus 70)	Non-seasonal Fecal-oral route as predominant mode of transmission
Adenovirus	Several different syndromes – Upper and lower respiratory diseases, keratoconjuntivitis, hemorrhagic cyctitis and gastroenteritis with diarrhea.	Seasonal peaks in winter and spring-depending on strain circulating

b) New Discovered Viruses /Unknowns

Rapid and state of the art diagnostic tools have made it possible to identify new viruses in the lower respiratory tract. Some of the pathogens identified were previously undiagnosed infection (Hustedt, 1993). Investigations were hindered as it was difficult to collect appropriate lower respiratory specimens (Garbino, 2004). A summary of the new emerging /unknown viruses is given in Table 7.

Table 7 Summary of the new emerging /unknown viruses

Etiologic agents	Disease
Bocavirus	It was first discovered in 2005. It was classified in the family of Parvoviridae, subfamily Parvovinae, genus Bocavirus. Allender et al first showed that Bocavirus can be present in gastrointestinal tract in children with or without respiratory symptoms. Like other newly identified virus, there is no in vitro culture system.
Metapneumovirus	Van den Hoogen isolated the first human metapneumovirus from children experiencing RSV-like symptoms in 2001.The seropositivity is almost acquired in virtually all children by the age of 5 years of age.
Rhinovirus C	A variant rhinovirus has also been detected and shown to cause severe pneumonia. Rhinovirus, the most prevalent human respiratory pathogen, has in the past traditionally been attributed as a cause of upper respiratory tract infections, mostly common cold and concomitant acute otitis media episodes in infants and children. The recent detection, of rhinovirus species in its association with severe respiratory disease has strengthened and remotivated research interest in the clinical impact, molecular biology and epidemiology of this virus.

Influenza virus H1N1	A new strain of virus as a result of reassortment of viral genes from various different sources. High density of human population co-mingling with animals from livestock activity (such as large concentration of pig farms and poultry) facilitates this process. The swine, known as an excellent blender mixes flu virus of different sources (Walsh,2011).This re assortment process was responsible for the emergent of the regional epidemic or global pandemic Influenza virus A H1N1 in 1918 , 1957 and 1968 as well as the deadly influenza virus H1N1 in 2009 (Osterhaus,2008) . During the assortment activity, exchange of genetic materials took place producing these new strain of virus.
SARS coronavirus	Since the discovery of SARs coranovirus, there have been renewed interest in this virus and novel coranovirus have recently been discovered. These include coranovirus NL63 (discovered in 2004) and HKU1. In 2003, the pandemic severe acute respiratory syndrome (SARS) was caused by a new emerging variant strain SARS coronavirus. It is now recognized that this strain had likely evolved from newly recognized animal SARs like coronavirus. The reservoir host of this animal like SARs are bats and it is believed through small mammals, man became the incidental host via international travel , this variant was transmitted to 26 countries within a span of 9 months. 8098 people were infected and 774 deaths were reported to WHO before the epidemic was declared over in July 2003 (Long,2008).

It is believed with improved state of the art diagnostic tools, more new pathogens previously undetected may be discovered. The detection of these viruses in respiratory samples suggests a viral contribution to respiratory symptomatology and pathology. Extensive research to discover new viruses is needed to close the gap of undiagnosed lower respiratory tract infections.

VIRAL INFECTION CAN BE FATAL

Viral infection of the lower respiratory tract most often is benign; however occasionally it can be fatal as described in our case report (Norlijah Othman et al, 2005). This was a five-year-old, previously well obese girl, presented with acute shortness of breath after a history of 'flu-like illness'. She was hyperglycaemic (condition in which glucose level in blood is high) and went into shock shortly after admission. The initial impression was diabetic ketoacidosis for which she was given fluid resuscitation. The hyperglycaemia was transient; it reverted to normal level without the administration of insulin infusion, the therapy for diabetic ketoacidosis.

She rapidly deteriorated into hepatic failure, pancreatitis, myocarditis in heart failure and renal failure within 48hours of admission before she eventually succumbed. The only positive result was PCR for Enterovirus from the throat and rectal swab. The patient was thoroughly investigated for the possibility of infection, drug overdosage and metabolic disorder to establish the cause of this patient's fatal clinical course. The only positive result was the polymerase chain reaction (PCR) for non-enterovirus 71, which was obtained on both throat and rectal specimens, suggesting a possible diagnosis of a coxsackie infection.

Enteroviruses of human origin include polioviruses, coxsackie viruses of group A (types 1-24), coxsackie viruses of group B types 1-6, echoviruses (1-34) and enteroviruses (types 68-71). Most of these enteroviruses occur sporadically and are usually benign, although association with fatal cases is well documented. The unique clinical features of our case such as the rapidly fatal nature of the illness in the presence of myocardial failure and hyperglycemia mimicked to a certain extent the fatal cases reported during the 1997 Malaysian outbreak of hand, foot and mouth disease attributed to EV 71 (K Shekar, 2005).However, the overwhelming simultaneous multiple organ involvement with a positive enterovirus but negative EV71 laboratory findings were in favor of the diagnosis of a non-EV 71 infection, possibly a coxsackie virus as it is known to cause pneumonia and hyperglycaemia with destruction of the β-islets of the pancreas.

As a learning point, this report emphasizes the diversity of manifestations with fatal outcome in a viral infection involving the respiratory tract, even in a previously healthy child.

Viral Etiology and Clinical Features of Acute Lower Respiratory Tract Infections in Malaysia

This is the first study of an almost complete panel of the respiratory viruses using highly sensitive molecular methods among Malaysian children (N Othman, 2012). Previous local studies have used serology and the panel of viruses studied was on traditional ones. In this study the epidemiology, demographic and clinical features of respiratory viral infections were investigated among children less than five years hospitalized with acute LRI to Hospital Serdang, Malaysia. The cross-sectional survey was conducted at two 28-bedded pediatric wards, in Hospital Serdang, a government-

funded multi-specialty hospital in the state of Selangor, Malaysia. Participants were children more than one-month-old and less than 5 years of age who were admitted to the hospital from June to December 2009 with the diagnosis of acute LRI.

A panel of viruses was studied using molecular method-polymerase chain reaction (PCR) from the nasopharyngeal samples in children with acute LRI. The samples were detected for the established old viruses (RSV, rhinovirus A & B, parainfluenza1-4, influenza A & B, adenovirus and enterovirus) and the new, reemerging viruses (bocavirus, metapneumovirus, rhinovirus C and coranovirusOC43 & 229E). All patients were investigated for presence of bacteria (bacterial culture) and Mycoplasma serology.

Children who met the final diagnosis for acute LRI were included in the study. However, children were excluded from the study if they had one of the following exclusion criteria: those with congenital or acquired immunosuppressive conditions; patients with conditions posing a potential hazard in obtaining the nasopharyngeal samples.For the majority of cases, chest x-rays were performed, reviewed and reported by an experienced radiologist.

Patient Demographic Characteristics

A total of one hundred and sixty five children were included in the study. Nearly in all virus groups male predominance was observed, supporting the other studies that acute respiratory infections are more common among males than females (overall male: female ratio 1.82:1). Majority of the patients were Malay (92.1%) followed by Chinese (4.8%) and Indian (3.0%).

The mean age of the patients was 11.7 months, 64% in the first year of life (majority in the second half of the year) and 25% in the second year of age. The current study concurs with findings from

other studies that show the burden of hospitalization from viral LRI is 90% among young children <2 years old. Nearly one third of the enrolled children had at least one underlying co-morbid condition and asthma comprised of almost half of these patients.

Prevalence of Respiratory Viruses Among Children with LRI

Of 165 samples tested, at least one respiratory virus was detected in 158 of the 165 children implying a detection rate of 95.8%.The detection rate was extremely higher than those previously reported locally (Chan,1999; Zamberi, 2003) as the current study employed a more sensitive PCR method rather than serology to investigate the viral etiology for acute LRI. Furthermore, the previous studies were only confined to the old viruses, unlike the more extensive panel of viruses as in our study. However, Katherine E et al (2009) similarly reported a high detection rate of 89.9% using PCR on predominantly pediatric patients with acute respiratory infections in Brisbane.

Table 8 shows virus frequencies. Single virus was detected in 114 (67.9%) patients; 46 (27.9%) were co-infected with different viruses including double-virus infections in 37 (22.4%) and triple-virus infections in 9 (5.5%) cases.

Table 8 Virus frequencies

Virus	Total infection
RSV	83 (50.3)[a]
HRV	54 (32.7)
HAdV	24 (14.5)
HMPV	16 (9.6)
IFV-A	15 (9.1)
PIVs	8 (4.8)
PIV-1	1 (0.6)
PIV-2	3 (1.8)
PIV-3	4 (2.4)
HBoV	6 (3.6)
HCoV-OC43	4 (2.4)
HEV	3 (1.8)

Our study showed that RSV is still the commonest virus causing acute LRI (Etamedi MR, 2012) followed by rhinovirus and adenovirus in our local community. Previously, published findings have frequently confirmed RSV to be the major viral pathogen associated with LRI in children in both tropical and developing countries [WHO; 2009, Martin W, 1998].Rhinoviruses were also found to be associated with acute LRI at a relatively high rate, contradicting the traditional notion that this virus is mainly confined to upper respiratory infections. In constrast, bocavirus, coronavirus and parainflueza viruses were present at a low prevalence. We also reported for the first time the two new viruses, metapneumoviruses, bocavirus, (Etemadi MR et al 2011), rhinovirus C as possible causes of acute LRI among children in Malaysia (Etemadi MR, 2011).

Seasonal Distribution

The monthly distribution of cases with respiratory tract viruses is shown in Figure 11 and Figure 12. During the study period a continuously persisting activity was seen for RSV, rhinovirus, adenovirus and metapneumovirus. Outbreak of influenza A was from July to September, and peaked in August and plateaued from September onwards. RSV and rhinovirus peaked in October, an increase of cases was seen after the cease of the outbreak of influenza from September onwards. For the viruses with low prevalence, no distinct pattern is seen.

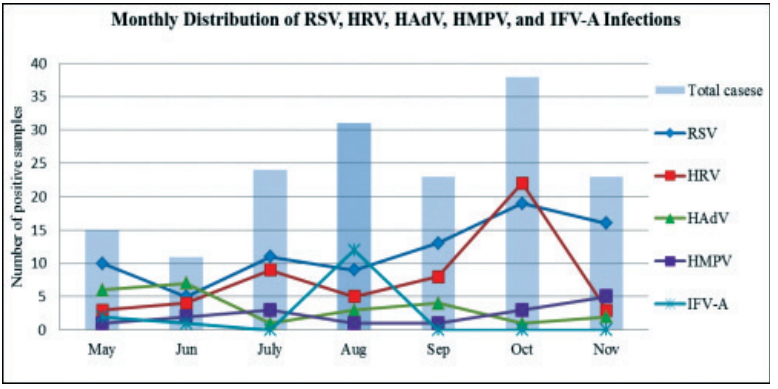

Figure 11 The monthly distribution of cases with respiratory tract viruses: RSV, HRV, HMPV and IFVA

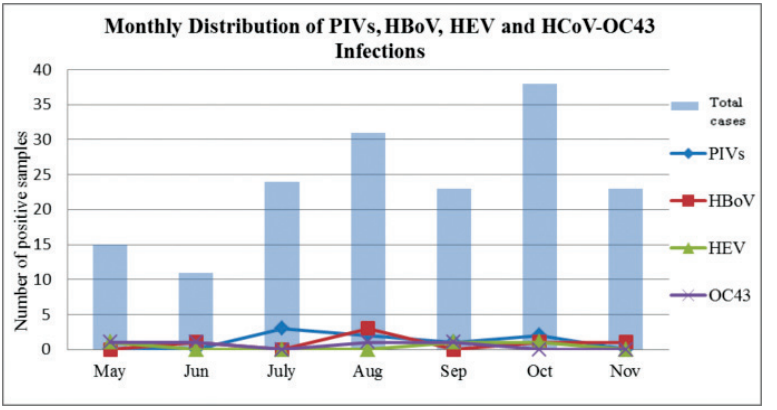

Figure 12 The monthly distribution of cases with respiratory tract viruses: PIV, HBOV, HEV, HCO-V

Clinical Characteristics

The clinical features of children who were tested for these viruses are summarized in Table 8. The age distributions of infants and children associated with each virus differed. LRI caused by RSV were predominant among younger infants (mean age, 9) compared with LRI associated with rhinovirus, metapneumovirus and influenza. In particular, a greater proportion of RSV infections occurred in infants <6 months old, compared with other virus-associated LRI. In addition, rhinovirus accounted for a large proportion of infants in the second half of the year. In contrast, influenza was frequently detected in older children of more than 1year old.

The main clinical features of viral acute LRI are as shown in the bar chart (Figure 13). The more common clinical presentations found were cough (96%), fever (85%), rhinorrhea (83%), difficulty in breathing (84%), tachypnea, chest wall crepitations (93%) and recession (80%). Vomiting was the main non-respiratory symptoms in about half of the patients in this study population. As expected,

these features were no different from acute LRI caused by other non-viral pathogens such as bacteria. Fever, rhinorrhea and cough are also not specific for acute LRI as probably they are also present in upper respiratory infections (Kusel MMH, 2006).

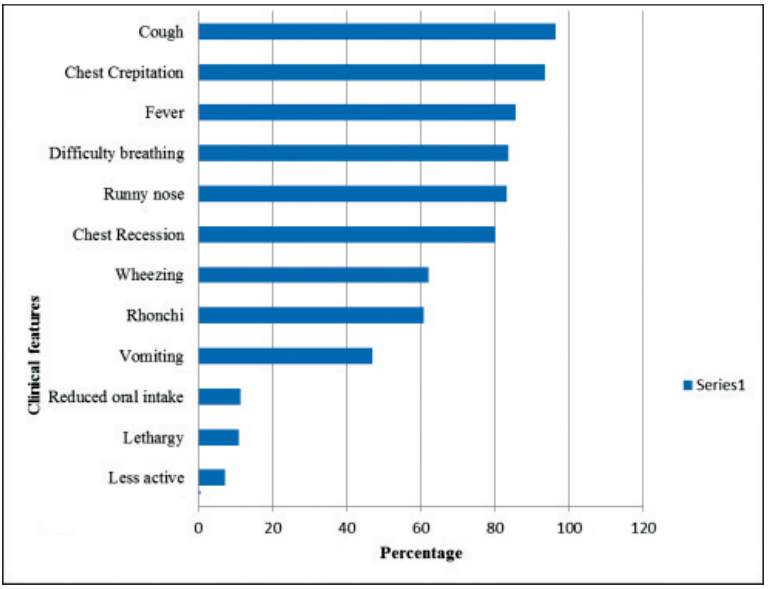

Figure 13 Distribution of clinical features of study population

Children were admitted to the hospital after a mean duration of 3 days after the onset of clinical symptoms which is consistent with other studies (WHO, 2009, Martin W, 2008). Our study showed that children infected with rhinovirus were hospitalized earlier in the course of their disease and were also less febrile on presentation as compared to the other highly prevalent infections-RSV, metapneumovirus and influenza. The possible explanation for this observation is rhinovirus has shorter incubation period as compared with the other viruses. It is also the least invasive with

minimal cell damage and consequently secondary bacterial infection is far less a complication. As a result, patients with rhinovirus were less febrile and subjected to lesser antibiotics, thus stayed shorter in the hospital as seen in this study.

In the current survey, we found that patients infected with influenza seem to have more prominent symptom of diarrhea as compared to the other viruses. This could be attributed to the more systemic nature of this infection with direct invasion of the gastrointestinal system by the virus. The frequency for rhonchi (these are lung sounds, described as low-pitched sounds that resemble snoring and implies airway obstruction) was the same for all the viruses, whereas crepitations (these are lung sounds, described as a dry sound like that of grating the ends of a fractured bone) occurred more frequently in patients infected with metapneumovirus and influenza as compared to RSV or rhinovirus. These latter lung sounds (crepitations) were heard in all the low prevalent viruses in this study.

In terms of laboratory findings, the white cell (a blood test to measure the number of white blood cells, a type of cell in the blood to fight against infection) and neutrophil cell counts (a type of white cell count that fights against infection) were higher in rhinovirus infection than in the RSV metapneumovirus and influenza. However, these abnormal blood counts may not reflect secondary bacterial infection in rhinovirus infection. Several studies in the past, acknowledged the increase neutrophils as a risk to development of asthmatic exacerbations.

In this study, half of the chest X-ray was reported as abnormal. The low rate of abnormalities detected may be explained by the fact that chest x-ray may not be sensitive enough to show the whole profile of lung infiltrates as seen in adults with pneumonia (Lehtinen et al, 2007). A discrepancy between clinical and radiological

pneumonia was also observed in study by Peiris (2003) and it may represent the subjectivity of clinical observation. Peribronchial thickening (thickening surrounding the airway) is the most frequent findings as it denotes viral infection. In agreement with Wolf (2006), Calvo (2010) and Mullins (2004) the frequency of abnormal findings was similar among the different virus groups and no distinctive differences were noted.

Hospital Course

Oxygen was administered to almost three fourths of the patients which were found higher than that the previous literature (Miller E, 2007). It seems possible that the higher frequency need for supplemental oxygen could be the presence of more patients with underlying medical condition in the study population. Another possibility may be due to the occurrence of bacterial culture-negative co-infections. Three of the patients required ventilation for 3-7 days; two had single infection of rhinovirus and RSV respectively while the other has dual RSV and adenovirus infection. No death was reported in this study.

The most common discharge diagnosis among all the children infected was pneumonia, followed by bronchiolitis. RSV followed by rhinovirus was more likely to cause bronchiolitis, and metapneumovirus followed by influenza showed a tendency to cause pneumonia. RSV is known traditionally as the major cause of bronchiolitis in children, whereas the importance of rhinovirus in contributing to the etiology of LRI has emerged over the past one decade with the introduction of PCR as a diagnostic research tool. Metapneumovirus, the new emerging virus, has also been increasingly recognized on its role in LRI. Previous studies has shown varying burden of this new virus as a cause of pneumonia

or bronchiolitis. The differences in observation could reflect differences in diagnostic definitions or study populations between reports.

CONCLUSION

Our results suggested that respiratory viral agents significantly contributed to the etiology of acute LRIs among hospitalized children. Majority occurred among children less than 2 years of age demonstrating the notion that the burden of respiratory infections is high among this age group of patients. RSV is still the commonest virus causing acute LRI followed by rhinovirus in our local community. The new viruses such as metapneumovirus and bocavirus also contributed to the causes of acute LRI.

PCR method employed in this study permitted the detection of many viruses and allows us to have a broader insight of the viruses implicated in LRI. Our study has limitations. It was based on an analysis of samples from cases with acute LRI in a hospital based. Therefore we could not determine the population-based prevalence. Other limitations include there was no control and a qualitative assay rather than quantitative was used. This may not reflect the true incidence of the actual infection as some viruses are known to harbor in the respiratory tract for a long time, without causing infection.

OTHER PATHOGENS

A variety of organisms and host factors prompt consideration of specific organisms. The most important of these is *Mycobacterium tuberculosis* (MTB), which should always be suspected if there is a history of exposure, in the presence of typical chest x-ray changes compatible with the infection (eghilaradenopathyie lymph

enlargement around the hilar area of the lungs) or when pneumonia does not respond in a typical fashion to therapy or with passage of time.

MTB in Children

Tuberculosis (TB) is usually a primary disease of children, and the dissemination of the infectionwith its attendant risk of mortality can be rapid. Early diagnosis is very important but unfortunately difficult. The "gold standard" method of diagnosis of TB is culture. Unfortunately, this is rarely obtained in children with TB disease because of the paucibacillary nature of the illness. Furthermore, a culture takes a longer time, which limits its usefulness in the initial diagnosis. At best, only 30-50% of cases of tuberculosis in children are confirmed by culture (Shingadia and Novelli, 2003), while 30% could be Mantoux negative (Lokman, 1994). Furthermore, the lack of characteristic symptoms in a majority of children, in comparison to adults, makes TB difficult to be diagnosed in the former group.

In an endemic area such as Malaysia, a diagnosis of TB should always be entertained in a clinical setting when there is poor clinical response to conventional anti-microbial therapy. Even with an unusual presentation (Norlijah O, 2007), in the presence of a negative culture and Mantoux as well as in an absence of contact with other tuberculous patients, TB infection should also be considered as a possible infection. In such a clinical scenario, TB PCR is a useful adjunct tool for a definite diagnosis. (Norlijah O et al, 2006). It is rapid, highly specific, although less sensitive, especially from sterile body fluids and can add to the overall decision-making process when considered in tandem with appropriate clinical findings.

Clinicians should be more perseverant and open in the pursuit of the diagnosis; otherwise, delayed diagnosis and treatment could be detrimental to a patient's life, leading to increased morbidity and

mortality. Furthermore, TB has been under-diagnosed in endemic countries such as Malaysia, because most young doctors expect the skin sensitivity or smear for AFB tests to be positive before treatment would be initiated. Such practices have resulted in 30% of TB deaths to be diagnosed at post-mortem (Hooi, 1994)

Pertussis

Pertussis is a highly contagious bacterial disease of the respiratory system caused by *Bordetellapertusis*. In some countries, this disease is commonly called whooping cough, is also called the 100 days' cough or cough of 100 days. It mainly affects infants younger than 6 months old before they're adequately protected by immunizations, and children 11 to 18 years old whose immunity has started to fade

Initial symptoms, similar to the common cold usually develop about a week after exposure to the bacteria. Severe characteristic episodes of coughing, which last for one to two minutes, typically described by mum 'the face of her child turning red or purple'. This coughing spells start about 10 to 12 days later. In a more life threatening episode, the child may actually stop breathing (called apnea) for a few seconds during these particularly bad spells. In older children, the coughing often ends with a "whoop" noise. The sound is produced when the patient tries to take a breath. The whoop noise is rare in patients under 6 months of age and in adults. Coughing spells may lead to vomiting or a short loss of consciousness. Pertussis should always be considered when vomiting occurs with coughing, and in the presence of the classical characteristic cough especially in children with incomplete immunization (Norlijah O et al, 2005). Adults and teens with whooping cough may have milder or atypical symptoms, such as a prolonged cough (rather than coughing spells) or coughing without the whoop.

Many experts believe that the medication is most effective in shortening the duration of the infection when given in the first stage of the illness, before coughing spells begin. But even if antibiotics are started later, they're still important because they can stop the spread of the pertussis infection to others. Infants and younger children are more likely to be hospitalized because they are at greater risk for complications such as pneumonia, which occurs in about 1 in 5 children under the age of 1 year who have pertussis.

Before a vaccine was available, pertussis killed 5,000 to 10,000 people in the United States each year. Now, the pertussis vaccine has reduced the annual number of deaths to less than 30. But in recent years, the number of cases has started to rise. By 2004, the number of whooping cough cases spiked past 25,000, the highest level it's been since the 1950s.

Fungal Infections

In immunocompromised children, fungal infections should be highly considered as a cause of pneumonia. It can be caused by either endemic or opportunistic fungi or a combination of both. Case mortality in fungal pneumonias can be as high as 90% in immunocompromised patients, though immunocompetent patients generally respond well to anti-fungal therapy.

Residence in or travel to certain geographic areas suggests consideration of certain pathogens. *Coccidiides immitis* is endemic in the Southwest United States, northern Mexico, and parts of Central and South America. *Histoplasma capsulatum* is endemic in United States and Canada. *Pneumocystis jirovecci* (P. carinii) causes pneumonia in HIV-infected infants at 3-6 months, in severely malnourished children and immunocompromised hosts. *Penicillium marneffei* is reported predominant in Thailand and

particularly Thailand where it has become the third defining illness defining AIDS. Due to the lagging behind of the AIDS epidemics in Malaysia as compared to Thailand, penicilliosis cases are seen sparingly especially in children (O. Norlijah, 2004)

Other Rarer Pathogens

Pseudomonas pseudomallei (melioidosis) is of public health importance in endemic areas, particularly in Thailand, Malaysia and northern Australia and the organism is found in soil and water (Norlijah Othman, 2007). Some other pathogens, Chlamydophiliapsitaci, Coxiellaburnetii and Francisellatularensis are infected from infected birds, animals or humans. Legionella pnemophila is a rare cause of pneumonia in children but is considered with certain environmental exposures and in immunocompromised individuals. Pneumonia in leptospirosis, on occasion may be dramatic and is associated with a more severe form of infection with multiple organ involvement (Norlijah Othman et al, 2007).

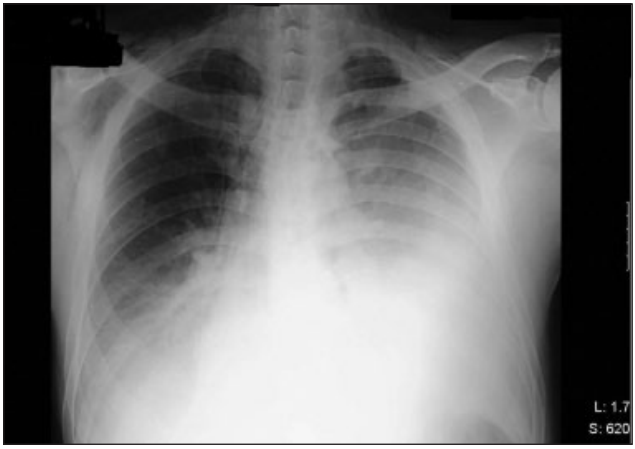

Figure 14 Chest x-ray showing bilateral effusion; the child with leptospirosis

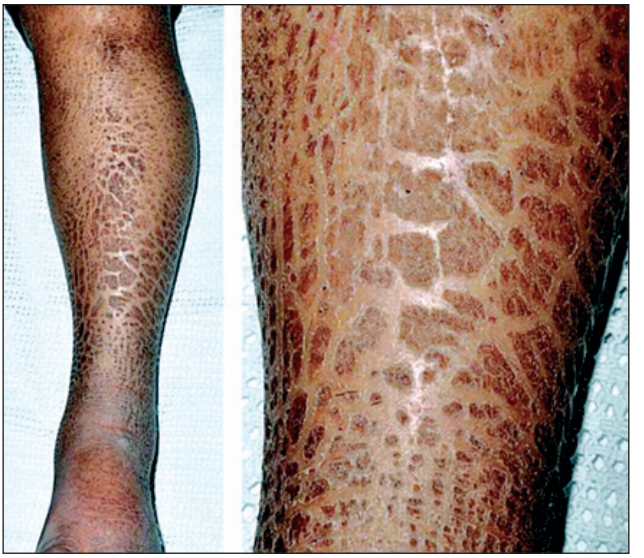

Figure 15 Icthyosis, a skin condition, first case reported associated with leptospirosis

Typhoid, a common worldwide bacterial disease, transmitted by the ingestion of food or water contaminated with the feces of an infected person, which contain the bacterium *Salmonella typhi*, rarely causes pneumonia (Othman N, 2003).

FUTURE DIRECTIONS-THE WAY FORWARD

Lower respiratory infections continue to threaten the health of children worldwide as it continues to be the major killer in children, especially in developing countries. It is estimated that 3.9 million children die each year from acute respiratory infections (WHO, 2009).This large mortality, which virtually goes unnoticed, has been described as being equivalent to a jumbo jet carrying 400 children crashing every hour, day after day. The outcomes of LRI illness

are far better in developed countries, but the overall morbidity of LRI is still high and may exceed that of other age groups. It is also clear that further progress in preventing, diagnosing and treating LRI diseases will have an impact on the health of a child.

There is still a gap in information on the burden of LRI in developing countries as compared to developed countries. LRI are much studied in developed countries and their impact on health care is well understood. From the public health point of view, it would be valuable to know the causative agents, what their disease manifestations are, what interplay between viruses and bacteria and to institute intervention strategies to prevent future infections. It is now the time to plan studies that would determine the burden of LRI in the developing world. The ongoing PERCH (Pneumonia Etiology Research for Child Health), a comprehensive multinational study, evaluating etiology of pneumonia and its associated risk factors is an on-going multi-centred (at seven sites) worldwide study, will throw some light on this problem in the near future(Gilani Z et al, 2012).

Standard care management has been the primary strategy suggested by WHO for reduction of pneumonia mortality (Stephen MG, 2008). The simple guidelines developed by the WHO for early detection and treatment of pneumonia have been tested to reduce acute LRI mortality in children, but not adequately utilized. Delayed in seeking medical treatment by parents/guardians and failure to recognize LRI signs/symptoms in children by medical practitioners/ health workers are the reasons for the above strategy not to succeed in total.

The key dilemma for clinicians is to distinguish between bacterial and viral LRI disease(Jean EK, 2003). The great majority of respiratory infections are of viral origin. However, 10-50% of patients will develop secondary infections. Depending on the

clinical setting, various tests are may be available to evaluate a child with LRI disease. Yet no specific test, or panel of tests, consistently differentiates viral from bacterial LRIs. Moreover, co-infection with both virus and bacteria may occur. Clinical, radiological or non-specific laboratory findings are not sufficiently sensitive and specific for separating between viral, bacterial or atypical bacterial pneumonia, as observed in many population-based, hospital based outpatient and hospital-based inpatient studies (Mullins 2004, Wolf 2006, Calvo 2010). For that reason, studies continue to document the overuse of antibiotics for treatment of LRI's in children, especially those who are hospitalized (Niang et al, 2010). The widespread use of antibiotics likely reflects the clinical problem of differentiating bacterial from viral LRI disease, as well as the potential risks of bacterial LRI illness. Improved techniques to detect bacterial and viral pathogens remain a challenge for future researchers to ease the healthcare providers' burden in interpreting signs and symptoms of LRI diseases that are often clinically indistinguishable.

The difficulty in the identification of the causative agent of LRI in children remains challenging for a couple of reasons: endotracheal aspirates cannot be obtained routinely, nasopharangeal swabs only show colonization by normal flora including the bacteria most commonly causing pneumonia, and bacteremia is demonstrated in less than 10% of bacterial community acquired pneumonia.. Therefore, the etiology of LRI especially in pneumonia remains often unknown, with the consequence that many children get an antibiotic treatment from non-bacterial infections, contributing to the increase of bacterial resistance to antibiotics.

There is also a growing problem of resistance to antimicrobial agents and the spread of this trait is global. Examples are penicillin-resistant *S. pneumoniae*, emergence of vancomycin-resistant *S.*

aureus and multi-drug resistant tuberculosis continue to increase worldwide. The resistance pattern is not only confined to bacteria but of late atypical bacteria- macrolide-resistant *M. pneumoniae* and influenza virus- ometalvir-resistant to Influenza virus have been reported.

Various factors have been identified to be responsible for the emergence and spread of resistant microorganism. These include irrational and self-use of antimicrobials, lack of adherence to prescribed regimen, wide spread non-human use of antibiotics and other anti-infective agents, increased use of antimicrobials, especially antibiotics in immunocompromised and critically ill patients. The problem is further compounded by poor prescribing habit of doctors. The key factor is widespread, indiscriminate use of antimicrobials.

Increases in the incidence for antimicrobial resistant community acquired pneumonias pose a major challenge to health care providers. The resistant organisms are not only difficult to treat; they also impose great health risks to individuals and significant costs to society. The resistant organisms have the potential of spreading to non-hospital environments, so that the problem which was initially encountered in hospital settings is now increasingly a community problem as well. For this reason, the World Economic Forum has included antibiotic resistance in its 2013 Global Risks report recently.

Effective and rigorous surveillance system has been put in place in some countries to track emergence and spread of resistance to antimicrobials. Such surveillance has been able to bring about changes in national policies and practices. Other measures include generating grants for research to identify genetic mechanisms for antibiotic resistance, encourage pharmaceutical companies in search for new antimicrobials, judicious prescription and use

of antimicrobials and simple hygienic practices at home and particularly when visiting hospitals, such as hand-washing, are all key and important ways to formulate strategies to combat the increasing antimicrobial resistance.

With the availability of PCR, it is now possible to detect new pathogens such as metapneumovirus, bocavirus, the novel coronavirus and rhinovirus-C's, thereby allowing for better definition of certain LRI illnesses in the clinical setting. On the other hand, the clinical interpretation of the detection of a virus from nasopharangeal secretions in a child with LRI can be challenging. Viral quantification may prove helpful to determine when an isolate is associated with severe disease. Several superior molecular typing also differentiates CA-MRSA against HA-MRSA, which can be used for supporting nosocomial infections; in tracing the nosocomial sources and transmission routes of the bacterial pathogen.

Preventive Strategies

- Targeting vaccinations

  Vaccination against Hib and pneumoccocal diseases has shown an impact on the incidences of the related pneumonias in developed countries where extensive immunization is being implemented. The benefits from both vaccinations include: individual immunity from the disease, herd immunity from the disease, and simplified treatment regimens as antimicrobial resistance is being reduced. For instance, vaccine probe studies from developing countries with high disease burden from Hib infections have demonstrated a 20-30% reduction in "x-ray documented pneumonias in children less than 3 years old

vaccinated against Hib (Russel FM 2003, de Andrade Al, 2004)). The widespread use of both vaccines has already altered the spectrum of community acquired pneumonia in children, and more global use of these vaccines may reduce (or eliminate) the risk of antimicrobial resistant bacterial LRI. However, issues of cost and distribution of both vaccines to the developing countries remain the key obstacles for the vaccines to be available worldwide. Likewise, vaccines for other major causes of childhood pneumonia such as influenza will likely become more widely used across the globe or may be successfully developed (eg RSV) over the next decade, and therefore will further influence the pneumonia burden and remaining etiologies.

- Effective health education of the community and appropriate initiatives taken by the government to address the known risk factors including various socio-demographic, nutritional and environmental, associated with LRI, leading to a healthy community and nation well-being. Improvement in global socioeconomic conditions will influence the pneumonia etiologic spectrum in the future.

- Well-written policies to be in place for any outbreaks.
  While there is much scope for further research, it is also imperative that all efforts be made to effectively implement strategies which have been shown to have a definite impact on LRI mortality in order to reduce the high mortality especially in developing countries. The responsibility for this does not lie with the government agencies alone but requires the concerted and sincere effort of all those involved in health care.

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BIOGRAPHY

Professor Dr Norlijah Othman was born in Tampin, N. Sembilan in 1961. She received her formal education in Tunku Besar School and secondary education in Sekolah Menengah Sains Tunku Jaafar, Kuala Pilah. She was active in sports – a state netball player and actively took part at the district sprint events. Even at university, she continued to participate actively in games for the faculty. Her favourite subject has always been in Mathematics and she always wanted in her early days to take up a career in either actuarial science or computer. However, on persuasion from both parents, she took up Medicine instead and has never regretted making such a decision.

She completed her MBBS (Mal) at the University of Malaya in 1986. She obtained her MRCP (UK) at the Royal College of Physicians in United Kingdom in 1992. A young paeditrician at 30, she worked for a while in Bristol United Kingdom and later in Hospital Sultanah Aminah, Johor Bahru. Her special interest in Infectious Diseases, has driven her towards pursuing her subspecialty training as a fellow in Infectious Diseases in 1996 at the prestigious Great Ormond Street Hospital in London.

Upon returning from her subspeciality training, she was based in Institute of Paediatrics, Hospital Kuala Lumpur as the Head of Paediatric Infectious Disease in the hospital. During her short stint as a Specialist in Paediatric Infectious Diseases with Ministry of Health, she was involved in the setting of several existing national policies in relation to infectious diseases. Among the major ones include the setting up of the national policy for i) provision of antiretroviral therapy in HIV children and injectable (SABIN) and Hib vaccinations to be made available to these children and ii) perinatal maternal-child transmission in HIV (ACTG protocol), which was piloted in 1998 and now is part of the public health programme for antenatal mothers/babies. She was also very much

involved in the first major EV 71 outbreak in Malaysia, which started in Sibu, Sarawak in 1998. She was one of the collaborators of all acute fatalities in children during the outbreak in Peninsula Malaysia and was also responsible for drawing up a protocol for suspected fatalities during the outbreak period.

1999 was a major turning point in her career development when she joined Universiti Putra Malaysia as an Associate Professor and later promoted to a Professor in July 2007. She was the Unit/ Department Head from 2000 onwards. Being a pioneer, she has helped to establish the undergraduate Paediatric program and further improved it in the later years. Her other pioneering projects during her headship was organizing and establishing the Paediatric services both in Hospital Kuala Lumpur and later in Hospital Serdang.

In August 2010, she was appointed the Dean of the Faculty of Medicine and Health Sciences, an administrative post that she currently holds. During her Deanship, she has gained several accomplishments to her credit. She has helped to procure the RM600 million allocation for the new 400-bedded teaching hospital, set up the Family Medicine private clinic, put up the 5 new Masters Medicine program of the different fields mobilize the academic staff under on administrative centre and improved the working benefits and infrastructure for the betterment of the faculty and the staff. She has also intensified the community engagement program such as the Program Anak Angkat and Kem Kesihatan at Pagoh and Pasir Gudang.

As a Pediatric infectious disease specialist and being the first two to be formally trained in this area of subspecialty in the country, she has been one of the four committee members for the National Specialist Registrar since it was established. She has been responsible in formalizing the three-year training program for the country. She was appointed as a visiting consultant for National

Health Institute (IJN), providing consultations on infectious-related cases before she became the Dean in 2010. She had the opportunity to further her subspecialty training in three other renowned centres apart from Great Ormond Street Hospital. The others include University of Sydney, Australia, University of Chulalongkorn, Thailand and latest was University of John Hopkins, Baltimore, USA.

Despite her hectic schedule as a Dean, she still finds time teaching which she enjoys immensely in guiding the students, giving invaluable advice to them and mentoring them on 'hands on' examination on patients. She also finds it is a pleasure talking and communicating with her patients during ward-rounds. In terms of research, she was involved in 27 research projects where she was the project leader for 10 of these projects. In the field of publication, she has written in more than 100 publications. Her publications include among others 43 publications in journal, 55 proceedings at international and national level, 10 articles related to pediatrics in general in family magazines, and 4 modules. This does not include working papers/modules, which she is actively involved.

Professor Norlijah Othman, feels as an infectious disease specialist, there are more horizons to venture especially in terms of scope of research as Malaysia still lacks the basic data in this area. Research collaboration has to be intensified to yield more useful results. As a Dean of the Faculty, she is of the opinion that the faculty has a lot of potentials yet to be tapped and improved especially in terms of education & curriculum, research & publication internationalization, industrial linkages & community engagement and income generation. She believes the faculty can be one of the best in the region.

ACKNOWLEDGEMENT

I would like to take this opportunity to express my utmost sincere gratitude and appreciation to both my parents for their love, support and understanding. I would not have made it if it had not been for them.

To Prof Tan Sri Dato' Dr Nik Mustapha R. Abdullah, the previous Vice Chancellor, thank you , for giving me the chance to lead the Faculty of Medicine and Health Sciences. To Dato' Dr. Radin Umar Radin Sohadi , my immense gratitude for his ideas, advice and guidance. To Datuk Dr. Mohd. Fauzi Hj. Ramlan the current Vice Chancellor for your unfailing support-thank you.

To Prof Datin Paduka Dr. Aini Aderis thank you for being understanding, a good listener and advisor. She would always be the one I turn to if I needed someone to hear my indecisions. Being the Dean there were quite a number of these instances.

To Prof Dr. David Issacs, the Consultant Paeditrician in Infectious Diseases in Sydney Children's Hospital, Australia: thank you for coaching me. He gave me his complete trust to write my first paper. His trust was immeasurable because from that point, I knew how to write an academic paper. From a pure clinician to an academician it was so crucial.

To Prof Dato Sham Kasim, the first dean of our Faculty, thank you for taking me into UPM in 1999. I would not have been a member of the UPM staff if it had not been for his decision.

To MARCOMM and the special committee headed by En. Muhazam Mansor who worked very hard to organize this special inaugural event. To UPM Press, thank you for making this publication possible. My special thanks to Puan Kamariah Mohd Saidin and Puan Sahariah Abdol Rahim.

I take this opportunity to thank all my lecturers and staff especially in the Paediatric Department, co-researchers for sharing their thoughts, ideas, knowledge and experiences.

To all my collegues and staff at the Faculty of Medicine and Health Science. The list is innumerable- Thank You . Thank you and Thank you.

LIST OF INAUGURAL LECTURES

1. Prof. Dr. Sulaiman M. Yassin
   The Challenge to Communication Research in Extension
   22 July 1989

2. Prof. Ir. Abang Abdullah Abang Ali
   Indigenous Materials and Technology for Low Cost Housing
   30 August 1990

3. Prof. Dr. Abdul Rahman Abdul Razak
   Plant Parasitic Nematodes, Lesser Known Pests of Agricultural Crops
   30 January 1993

4. Prof. Dr. Mohamed Suleiman
   Numerical Solution of Ordinary Differential Equations: A Historical Perspective
   11 December 1993

5. Prof. Dr. Mohd. Ariff Hussein
   Changing Roles of Agricultural Economics
   5 March 1994

6. Prof. Dr. Mohd. Ismail Ahmad
   Marketing Management: Prospects and Challenges for Agriculture
   6 April 1994

7. Prof. Dr. Mohamed Mahyuddin Mohd. Dahan
   The Changing Demand for Livestock Products
   20 April 1994

8. Prof. Dr. Ruth Kiew
   Plant Taxonomy, Biodiversity and Conservation
   11 May 1994

9. Prof. Ir. Dr. Mohd. Zohadie Bardaie
   Engineering Technological Developments Propelling Agriculture into the 21st Century
   28 May 1994

10. Prof. Dr. Shamsuddin Jusop
    Rock, Mineral and Soil
    18 June 1994

11. Prof. Dr. Abdul Salam Abdullah
Natural Toxicants Affecting Animal Health and Production
29 June 1994

12. Prof. Dr. Mohd. Yusof Hussein
Pest Control: A Challenge in Applied Ecology
9 July 1994

13. Prof. Dr. Kapt. Mohd. Ibrahim Haji Mohamed
Managing Challenges in Fisheries Development through Science and Technology
23 July 1994

14. Prof. Dr. Hj. Amat Juhari Moain
Sejarah Keagungan Bahasa Melayu
6 Ogos 1994

15. Prof. Dr. Law Ah Theem
Oil Pollution in the Malaysian Seas
24 September 1994

16. Prof. Dr. Md. Nordin Hj. Lajis
Fine Chemicals from Biological Resources: The Wealth from Nature
21 January 1995

17. Prof. Dr. Sheikh Omar Abdul Rahman
Health, Disease and Death in Creatures Great and Small
25 February 1995

18. Prof. Dr. Mohamed Shariff Mohamed Din
Fish Health: An Odyssey through the Asia - Pacific Region
25 March 1995

19. Prof. Dr. Tengku Azmi Tengku Ibrahim
Chromosome Distribution and Production Performance of Water Buffaloes
6 May 1995

20. Prof. Dr. Abdul Hamid Mahmood
Bahasa Melayu sebagai Bahasa Ilmu- Cabaran dan Harapan
10 Jun 1995

21. Prof. Dr. Rahim Md. Sail
Extension Education for Industrialising Malaysia: Trends, Priorities and Emerging Issues
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