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Epidemiology and Diagnosis of Human Respiratory Syncytial Virus Infections

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1. Introduction

Respiratory syncytial virus (RSV) is a common winter time respiratory virus that affects persons of all ages. RSV was first isolated in children with pulmonary disease in 1957. Initially referred to as the 'chimp coryza virus', the nature of the virus to form syncytia (fusion of cells to form larger cells without any internal cell boundaries) in tissue culture subsequently resulted in the virus being named the respiratory syncytial virus. Formation of syncytia permits the virus to spread by evading host antibodies (Weir & Fisman , 2004)

Human RSV is a negative sense enveloped RNA virus and is a member of the family Paramyxoviridae, classified within the genus Pneumovirus. RSV has two subtypes A and B that are distinguished largely by differences in the viral attachment (G) protein or the nuclear (N) protein (Sato et al., 2005). During epidemics, either subtype may predominate, or both subtypes may circulate concurrently. RSV is unstable in the environment, readily inactivated by soap and water. The virus is spread through close contact with infected carriers or contaminated surfaces. Infection occurs when infected materials come in contact with the mucous membranes of the eyes, nose or mouth. It is possible that inhaled fomites are a source of infection. It can remain infectious on surfaces or fomites for 4-7 hours and can also survive on unwashed hands.

RSV is the main cause of bronchiolitis worldwide and can cause up to 70 or 80 percent of lower respiratory infections (LRIs) during high season. The lower respiratory tract includes continuation of the airways from the trachea and bronchi to the bronchioles and the alveoli (Henrickson, 2004). The common LRIs in children are pneumonia and bronchiolitis and the most common causes of viral LRIs are RSVs (Steweart et al., 2009). They tend to be highly seasonal, unlike parainfluenza viruses, the next most common cause of viral LRIs.

Environmental conditions such as temperature, relative humidity and UV-B radiation have been described in relation to RSV epidemics (Welliver, 2009). A study performed in Spain (Lapena et al., 2005) indicated that low temperature and low absolute humidity were positively associated with the number of RSV cases and low absolute humidity was independently related to RSV infection. Worldwide, RSV peaks at two temperature intervals: between 2-6°C in temperate regions and 24-30°C in tropical regions. RSV activity is greatest at 45-65% relative humidity and UV-B radiance inversely related to the number of RSV cases. The relation between RSV activity and low minimum temperature indicates that

this factor enhances virus transmission. It has been described in earlier studies that transmission of RSV is inversely related to temperature in cooler climates and this may be a result of increased stability of the virus in the secretions during the colder climate. Inactivation of RSV in air has been described (Rechsteiner & Winkler, 1969); stable aerosols of RSV were prepared and kept at different relative humidity. Virus recoveries were highest at high relative humidity and the stability of the aerosol was maximal at 60% relative humidity. This indicates that humidity indeed plays an important role and may affect transmission of the virus.

1.1 Children

RSV is the largest single cause of childhood hospitalization due to lower respiratory tract disease. Infections manifest themselves as mild upper respiratory tract infections or lower respiratory tract infections: bronchitis, bronchiolitis, and pneumonia. 10% of those infected require specialised paediatric care. High risk groups for severe RSV infection include premature infants, children with congenital heart disease, cystic fibrosis and other chronic lung disease (Stensballe, 2002). This may be due to the fact that immunity has not become fully established, narrow airways, incomplete development of the lungs and relatively short bronchial tree. It also affects the elderly and immuno-compromised patients. It has been estimated that RSV causes about 500,000 deaths in children each year globally (Shay et al., 1999). Although, mortality due to RSV is very low in Western Europe, the number of child deaths due to acute respiratory infections worldwide is considerable with 70% of deaths occurring in Africa and Southeast Asia (Nair et al., 2011).

• Cause of worldwide epidemics, which can occur annually or biennially
• Most children are infected by 3 years of age
• Responsible for about 70% of cases of bronchiolitis in children
• Re-infections occur throughout life and the same serotype can re-infect children and adults
• Associated with recurrent wheeze for many years after bronchiolitis
• Low birth weight is associated with acute respiratory infections in developing countries
• Cord blood vitamin D deficiency has been associated with Respiratory Syncytial Virus Bronchiolitis

Table 1. Characteristics of RSV infection

1.2 Adults

The elderly show increased susceptibility to respiratory infections and other related complications. In community dwelling, the elderly suffer fom 1.2 to 1.6 acute respiratory infections per year accounting for 25 – 50% of respiratory illness (Nicholson et al., 1997). RSV is a significant and unrecognized cause of seasonal respiratory tract infections (RTIs) in adults, accounting for as much as 25% of excess wintertime mortality usually attributed to influenza. Nearly 80% of RSV associated underlying respiratory and circulatory deaths occur among the elderly (Ramirez, 2008). RSV is estimated to account for about 180,000

hospital admissions each year exceeding. RSV is also recognized as an important cause of viral pneumonia in adults. Clustering of RSV infected patients on wards has suggested nosocomial spread by health care workers. Preventive measures such as handwashing are important, especially in hospitals and nursing homes where there may be many immunocompromised patients. During RSV season, it is advisable to minimize contact between high-risk patients and children.

2. Epidemiology of RSV Infections

RSV is highly contagious, it is thought that of half the infants that acquire RSV infection during the first year of life, approximately 40% of these infections result in lower respiratory infections. Virtually all children will have been infected by RSV by the first 3 years of life. RSV is associated with more deaths than influenza in children aged 1-12 months. Excess deaths due to RSV and influenza virus infection have also been reported for the elderly population.

2.1 Developed countries

Epidemics of the virus occur annually and tend to start in November or December and last 4 to 5 months. In any one year, about 90,000 children will be hospitalized due to RSV and 4,500 will die. RSV epidemic patterns differ by geographic locations. In the Northern hemisphere and particularly, within the United States, RSV mostly circulates between November and March (Dawson-Caswell and Muncie 2011). However, the severity of the season, peak of activity and time of onset can vary. Communities in the Southern United States experience the earliest onset of RSV activity. Midwestern States experience the latest. The national average duration is about 15 weeks and can range from 13 to 20 weeks (MMWR, 2010). The epidemic pattern of RSV is quite different in regions of Europe (biennial epidemics in alternating cycles of approximately 9 and 15 months) than in the Western hemisphere (annual epidemics). In Australia, about 100,000 infants are infected by RSV every winter. In temperate regions of Australia, the occurrence of annual winter epidemics has been well demonstrated (Mullins et al., 2003). The incidence peaks in July, with 55-77% of all cases occurring between July and September. Most of the cases of RSV infections in Australia occur in children under the age of 4 years. Mechanisms underlying the pathogenesis induced by RSV are mostly unknown. RSV induced bronchiolitis in infancy may predispose to asthma later in life (Ghildyal et al., 2003). In Germany, Finland, Switzerland, Sweden and Croatia, there is a two year RSV cycle repeating every 23 to 25 months. Unlike Europe, Great Britain experiences a monophasic, annual RSV epidemic cycle. In some parts of the USA, RSV cycles are also monophasic and annual (Milinaric-Galinovic et al., 2008)..

2.2 Developing countries

In developing countries, respiratory diseases represent a challenge to public health because of their severity, frequency, trends, and economic impact. Data from developing countries are even more limited in the ability to provide a clear estimate of disease burden. Published in 1998, a review of the literature on RSV in tropical and developing countries identified from ten longitudinal community-based studies that RSV was the etiological agent in 2% (in India)

to 73% (in Brazil) of lower respiratory infection episodes (Weber et al. 1998). Three studies (from Brazil, Uruguay, and Colombia) reported RSV as being the etiological agent in more than 50% of the community-based acute lower respiratory tract infection episodes. The authors identified the limitations associated with different methods used by the different studies to detect RSV. In general, studies that used immunofluorescence methods had higher rates of RSV detection, and the majority of the community-based longitudinal studies that had low RSV detection rates used culture alone. The same review examined the more abundant hospital-based studies in tropical and developing countries and found that RSV was detected in between 6 and 96% of cases of hospitalised lower respiratory tract infections. On average, RSV accounted for 65% of samples that were positive for a virus (range 27-96%); and 17% of acute respiratory tract infections in children admitted to hospital.

There is relatively scant information for the role of RSV in causing LRI among children in developing countries. Hence the WHO introduced standardized protocols for new studies to be undertaken in these regions. This was first performed in, Mozambique, Indonesia, Nigeria and South Africa (Robertson et al., 2004). The total incidence of LRIs occurring among children aged < 1 year was lowest in Indonesia and highest in Mozambique where 50% of children presented with an LRI and 13% were hospitalized. Among infants, RSV infections identified were 36% in Nigeria, 23% in Indonesia and 6% in Mozambique. For severe RSV attributable LRIs, the proportion was high in Indonesia but low in Mozambique. The rates of severe illness in children < 1 year in Indonesia, Mozambique and South Africa (15-16/1000 child years) are very similar to rates of hospitalization from industrialized countries eg. England (20/1000 child years), Germany (12/1000 child years), Norway (10/1000 child years), USA (20/1000 child years) and Austria (6/1000 child years). Differences in RSV rates in developing countries also depends on many social factors such fewer health centres, large families with many children facilitates more spread of infections. In some countries such as South Africa and Mozambique, the peak for RSV correlates with the presence or absence of rainfall.

2.3 RSV Infections in the Middle East

Little is known about the epidemiology of RSV infections in the Middle East and other desert climate regions of the world. The Middle East has large areas covered by desert. In summer, it is hot and can be very humid, whereas in winter, temperature can drop significantly. These weather variations can exacerbate respiratory infections (ARI) and chronic lung diseases in susceptible individuals especially asthmatics (Waness et al., 2011). Acute respiratory infections play a major role in hospitalizations in the Middle East. The number of children admitted with RSV diseases from developing countries in 2005 was more than double that estimated in 1986, and the incidence of RSV-acute lower respiratory tract (ALRI) was twice that of industrialized countries (Nair et al., 2010)

A review of RSV infections in the Middle East region (Table 2) shows that the occurrence of RSV infections is in the Winter season peaking around January as in other parts of the world, with the same age groups affected. This is in contrast to some developing countries eg. Indonesia, where the incidence of RSV LRI in the first 6 months of life is relatively low. Most cases of disease occur in older children (Simoes et al., 2011). A more precise

understanding of the timing of annual RSV epidemics should assist providers in maximizing the benefit of preventive therapies.

The current data on the load and importance of viral respiratory infection and hospitalization is scarce. Recipients of bone marrow transplant have been reported to have mortality rates over 50% with RSV pneumonia. Molecular epidemiologic studies have demonstrated that RSV nosocomial outbreaks often result from multiple introductions of distinct strains from the community. In Saudi Arabia a review of RSV hospitalizations showed that the majority of cases are due to bronchopneumonia, prematurity and lung, heart disorders (Al-Muhsen, 2010). In Jordan, RSV positive children require higher rates of oxygen use and longer hospital stay, which is a financial burden for poor countries (Khuri-Bulos et al., 2010). A study in Kuwait (Hijazi et al., 1997) found that RSV was the commonest agent identified in 52% cases of bronchiolitis, 29% of pneumonia and 51% of croup. Another study in Al Ain has shown that the clinical pattern of RSV infections includes bronchiolitis in 58% of cases, bronchopneumonia in 19% of cases and pneumonia 11%. RSV was strongly associated with cool temperatures and relative humidity between 50-60% (Uduman et al., 1996). The cycle of RSV infections is also less defined in the Middle East. In Saudi Arabia, the pattern appears to show regular rates of infection with a slower peak approximately at 3 years (Fig 1). Such trends need to be monitored and extended to other Middle Eastern countries.

Children younger than 60 days and those with severe symptoms may require hospitalization. Neither antibiotics nor corticosteroids are helpful for bronchiolitis. A bronchodilator trial is appropriate for children with wheezing, but should not be continued unless there is a prompt favorable response (Jafri, 2003). Frequent hand washing and contact isolation may prevent the spread of RSV infections. Children younger than two years at high risk of severe illness, including those born before 35 weeks of gestation and those with chronic lung or cardiac problems, may be candidates for palivizumab prophylaxis for RSV infection during the peak infection season (Lieberthal et al., 2006).

Recent studies have shown that Vitamin D deficiency in healthy neonates is associated with increased risk of RSV LRTI in the first year of life (Belderbos, et al., 2011). Vitamin D supplementation during pregnancy may be a useful strategy to prevent RSV LRTI during infancy. This could be particularly significant in Saudi Arabia and other developing countries where there is a high level of vitamin D deficiency among the population.

Hajj pilgrimage is a yearly event in which >2 million Muslims from around the world gather in Mecca, Saudi Arabia. Such high density of crowding presents a risk for local outbreaks and for worldwide spread of infectious agents. ARI is the leading cause of admission to Saudi hospitals during the Hajj (Ahmed et al., 2006). The close contact among pilgrims during periods of intense congestion, their shared sleeping accommodations (mainly in tents) and the dense air pollution all combine to increase the risk of airborne respiratory disease transmission. A viral etiology of upper respiratory tract infection (URTI) is most commonly implicated at the Hajj, but bacterial super infection often follows. More than 200 viruses can cause URTI at the Hajj. The main etiologies are RSV, parainfluenza, influenza and adenovirus (Rashid et al, 2008).

Country	Seasonality of RSV (Start)	Seasonality of RSV (End)	Prevalence of RSV in Lower Respiratory Tract Infection	Study Size (patient number)	Age Group affected	Authors
Saudi Arabia (Riyadh)	November	February	83%	883	<5 years	Akhter et al., 2008
Saudi Arabia (Qassim Region)	December	February	45.4%	282	< 1 year	Meqdam M et al 2006
Saudi Arabia (Abha Region)	November	February	40%	115	< 2 years	Al Shehri et al 2005
Saudi Arabia (Riyadh)	November	February	28.5%	256	< 5 years	Al Hajjar et al 1993-1996
Kuwait	October	March	36.8 %	1,014	< 1 year	Khadada M. et al 2010
Lebanon	December	May	26.7%	120	< 6 years	Hamze A et al 2007-2008
Jordan	December	March	12.5%	200	< 2 years	Al Toum R et al 2006
Turkey	January	March	29.5%	332	< 2 years	Kanra et al 2005
UAE	November	february	28.6%	252	< 3 years	Uduman SA et al 1993 - 1995
Qatar	November	February	59.9%	257	< 1 year	Wahab et al 1996-1998
Egypt	December	February	16.4%	91	< 5 years	Fattouh et al 2011

Table 2. Seasonality of RSV Infections Observed in the Middle East

Number of Patients	Predisposing factors	Age Range	Location	Treatment	Author
94	Premature, pulmonary pathology, neurological and cardio-vascular abnormalities	<1 year	Riyadh	Oxygen supplementation, bronchodilators, antibiotics	Al Muhsen, 2010
8	Pre term, ARDS	28 weeks	Riyadh	Mechanical ventilation, support	Kilani, 2002
412	Bronchopneumonia. broncihiolitis	< 5 years	Riyadh		Bakir et al, 1998
69		< 1 year	Riyadh	Supportive, antibiotics	Jamjoom et al, 1993
51	Prematurity, chronic lung diseases, atopic dermatitis, pure formula feeding, passive smoking	< 2 years	Abha	Supportive, Oxygen	Al Shehri, 2005
128	bronchopneumonia bronchiolits Coughing tachpnea	< 1 year	Qassim	antibiotics	Meqdam, 2006

Table 3. Characterisitics of RSV Infections in hospitalized Patients in Saudi Arabia

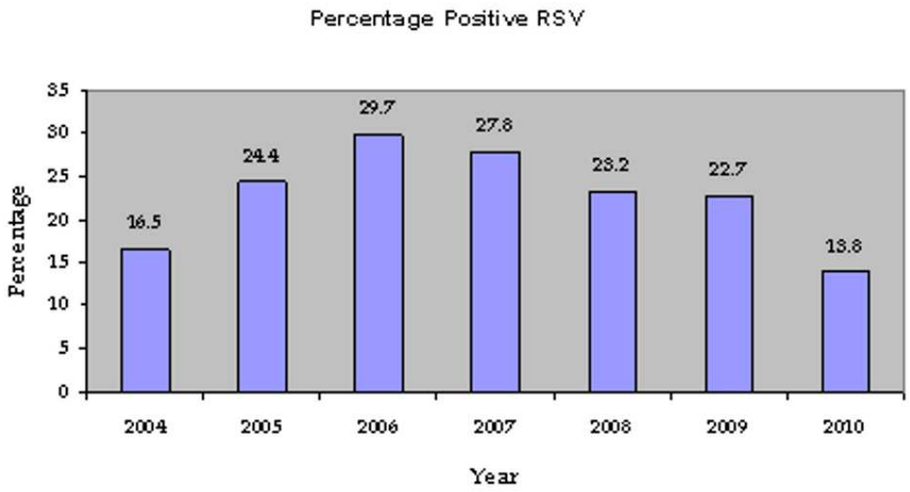

Fig. 1. Prevalence of RSV Infections between 2004 – 2010 at a tertiary Care Center in Saudi Arabia (Akhter, et al., 2008)

3. Laboratory diagnosis

Early diagnosis of RSV infection enables timely interventions to be introduced to control the spread of disease. Given the similarity in clinical presentation to influenza and human metapneumovirus, laboratory confirmation provides a definitive diagnosis of RSV infection. Clinical features of RSV infections overlap with other respiratory viruses so laboratory diagnosis is essential to establish diagnosis. Prior to the introduction of molecular diagnostics, respiratory viruses were primarily identified by virus isolation in tissue culture or antibody/antigen detection by serological methods: Specimens should be collected in the acute stage of the illness, kept moist, and refrigerated immediately.

3.1 Imaging studies

Chest radiography is frequently obtained in children with severe RSV infection. Chest radiography typically reveals hyperinflated lung fields with a diffuse increase in interstitial markings. In 20-25% of cases, focal areas of atelectasis and/or pulmonary infiltrate are also noted. Generally, these findings are neither specific to RSV infection nor predictive of the course or outcome, except for the observation that infants who have the additional findings of atelectasis and/or pneumonia may have a more severe course with their illness.

3.2 Clinical specimens

Nasopharyngeal aspirates (NPAs), swabs and washes are acceptable for culture, direct antigen detection and Nucleic acid testing (NAT) where this is available. Other acceptable specimens are endotracheal aspirates, bronchoalveolar lavage fluid and lung biopsy tissue. Swabs should be cotton, rayon or dacron-tipped, plastic-coated or aluminium shafted swabs. They should be placed into viral transport media and transported at 4°C or frozen at -70°C. Unacceptable specimens include Calcium alginate swabs or swabs in gel media, wooden swabs and dry swabs

3.3 Tissue culture methods

A cost-effective and relatively rapid approach to detecting RSV in humans is to use cell cultures in conjunction with immunofluorescence antibody (IFA) methods. Traditional cell cultures, while being sensitive, required long incubation periods. Recent advances have led to the development of enhanced cell lines that require shorter incubation periods but are also cocultivated (or contain mixed cell lines) to detect several viruses in the same culture vial (Lanley et al. 2007). The benefits of such cell line mixes in terms of providing a rapid and sensitive method for detecting respiratory viruses including RSV have been established, however, RSV detection is optimised by supplementing cell line cultures with the non-culture method of direct immunofluorescence Assay (DFA) (Leland and Ginocchia. 2007).

Viral culture is the gold standard by which other tests are compared. Specificity is not usually an issue; however, sensitivity in adults can be problematic. Adults generally shed lower titres and for a shorter period of time than children. Also, the virus is thermolabile and does not survive lengthy transit times. Culture is only 20 – 45% sensitive when compared with serology using acute and convalescent sera. The benefits of tissue culture are its broad sensitivity for a range of viruses, the necessity for infectious virus particles and its

relatively low cost. Human heteroploid cells, such as HEP-2 and HeLa generally provide the best tissue culture for RSV isolation. RSV produces a characteristic CPE consisting of syncytia formation and appears in 4 to 5 days.

Mixed cell line cultures were used for the first time at a tertiary care center in Saudi Arabia to accelerate virus isolation (Akhter et al). Rapid testing algorithms allowed all respiratory syncytial virus (RSV) isolates to be detected in one day, influenza isolates to be detected in 2 days, parainfluenza isolates within 3 days, and adenovirus in 2-5 days. 92% of RSV infections occurred in children one year and under. RSV infections occurred between November and February, with a peak in January. Influenza and adenovirus outbreaks occurred in November and December. Parainfluenza occurred in 2 waves, first in November and December followed by another peak in April. RSV appears to occur in a two year cycle similar to Europe (Fig 1)

3.4 Shell vial assay

Laboratory diagnosis of RV infections has become easier and more rapid with the use of centrifugation-enhanced shell vials (SV) as the culture method. Centrifugation of the clinical specimen onto cell monolayers followed by immunofluorescence detection and identification of viral antigens in SV cultures allows a much earlier diagnosis of infection. In this technique a small bottle (vial) with a removable round glass cover slip is used to grow the cells as a monolayer on the cover slip. Nowadays mixed cell types can be put in a single monolayer providing a variety of cell types for the virus to infect in a single vial. Once these monolayers are ready to be inoculated, the growth medium is removed from the vial and the clinical sample placed directly on the monolayer. The vial is then centrifuged, the clinical sample is removed and fresh growth medium is then added to the vial. It is possible, using this technique, to identify the presence of a virus before CPE occurs by using fluorescent monoclonal antibodies to detect early and pre-early proteins. The disadvantage of this method is it is not possible to do "blind passages". Some viruses may require longer incubation to adapt to the particular cell lines. Once used, the monolayer can not be re-incubated or re-inoculated as the fixed cells and viruses are not viable (Gleaves et al., 1984).

3.5 Antigen detection

Several ELISA kits are available for the detection of RSV antigens on a solid phase. ELISA techniques offer the advantages of objective interpretation, speed, and the possibility of screening a large number of specimens. Disadvantages include a generally poorer sensitivity and a "grey zone" of equivocal results, which requires confirmation by a time-consuming blocking ELISA procedure (Casiano et al., 2003). Both direct and indirect IF utilizing either polyclonal or monoclonal antibodies are available which possess a high degree of sensitivity and specificity. The general sensitivity of IF is 80 - 90% and for monoclonal antibody 95 - 100% (Aldous et al., 2004). IF techniques are fast and easy to perform but the interpretation of results is subjective and the specimen must contain adequate nasopharyngeal cells. Detection of RSV antigens in respiratory secretions by IFA or EIA is widely used in children and removes the need to recover infectious virus but requires a significant viral load to generate a positive result. Hence, these methods are not suitable for adults as studies have shown positive rates of only 23% by IFA and 10% by EIA.

3.6 Serology

Serologic diagnosis requires paired serum specimens in most instances and is intrinsically slower than direct methods. A variety of serologic techniques are used to measure antibodies, including neutralization, hemagglutination inhibition, complement fixation, and enzyme-linked immunosorbent assay (ELISA). Measurement of complement-fixation antibodies is generally less sensitive than the other methods and does not provide a serotype-specific diagnosis. Immunocompromised hosts often fail to develop diagnostic increases in antibody titers. RSV infections reoccur throughout life diagnosis can be demonstrated by a greater ≥ 4 fold increase in RSV specific IgG. When baseline sera are available, this method is ≥ 90% sensitive for diagnosis of RSV infection in the elderly. However utility of serology is limited to its retrospective nature (Falsey et al., 2003).

3.7 Molecular methods

The principal amplification technique used for RNA viruses is reverse-transcriptase polymerase-chain reaction (RT-PCR). Detection of RNA viruses requires an additional first step in which RNA is reverse transcribed to complementary DNA before PCR amplification. Theoretically, this technique is capable of detecting a single virus within 24 hours. Detection of the amplified sequence may be done at the reaction endpoint, or by continuous monitoring (real-time PCR). Real-time PCR has the advantage of allowing the virus to be quantified (Whiley et al., 2002).

Multiplex PCR methods have been developed that allow the detection of more than one nucleic acid sequence, and therefore more than one virus type, in the same assay. These are based on the principle that products of real time cyclers can be detected simultaneously at different wavelengths of fluoresence. Other nucleic acid amplification methods have also been developed, notably nucleic acid sequence base amplification (NASBA). This technique is also known as isothermal amplification, as it does not require the repeated temperature cycling used in conventional PCR methods (Beck & Henrickson, 2010).

The advantages of PCR and related methods are considerable. The main benefit is time saving allowing hours to a result rather than several days as for a cell culture assay. PCR also requires less operator skill and training to carry out and can be automated to process large numbers of samples. It is also extremely sensitive, although it can be vulnerable to contamination and cannot distinguish infective viruses. Most PCR methods require some costly equipment and are not suitable for use outside the laboratory. Non-quantitative PCR results may also be difficult to interpret, since low numbers of virus that do not signify an infection may be detected, but this problem is largely overcome by real-time PCR. Molecuar methods can also detect several orders of magnitude less than tissue culture methods (Borg et al., 2003).

3.8 Microarrays

DNA microarrays used as 'genomic sensors' have great potential in clinical diagnostics. Microarray analysis has the capability to offer multiplex detection, Multiple microarray platforms exist, including printed double-stranded DNA and oligonucleotide arrays, in situ-synthesized arrays, high-density bead arrays, electronic microarrays, and suspension bead arrays (Wong et al., 2007). In general terms, probes are synthesized and immobilized as

discrete features, or spots. Each feature contains millions of identical probes. The target is fluorescently labeled and then hybridized to the probe microarray. A successful hybridization event between the labeled target and the immobilized probe will result in an increase of fluorescence intensity over a background level, which can be measured using a fluorescent scanner. Biases inherent in random PCR-amplification, cross-hybridization effects, and inadequate microarray analysis, however, limit detection sensitivity and specificity (Miller & Tang, 2009).

3.9 Emerging technologies

There are several emerging molecular assays that have potential applications in the diagnosis and monitoring of respiratory viral infections (Takahashi et al., 2008). These techniques include direct nucleic acid detection by quantum dots, loop-mediated isothermal amplification; multiplex ligation-dependent probe amplification, amplification using arbitrary primers, target-enriched multiplexing amplification, pyrosequencing, padlock probes, solid and suspension microarrays, and mass spectrometry (Wu & Tang, 2009). Several of these systems already are commercially available to provide multiplex amplification and high-throughput detection and identification of a panel of respiratory viral pathogens. Further validation and implementation of such emerging molecular assays in routine clinical virology services will enhance the rapid diagnosis of respiratory viral infections and improve patient care.

Method of Detection	Advantage	Disadvantage
Virus Culture	Characteristic syncytial CPE allows identification Broad sensitivity	Time-consuming Need confirmatory identification method Requires expertise to maintain cell lines
Antigen Detection (IFA and EIA)	Commercial kits widely available Rapid ID Suitable for screening large numbers	Can give false results Does not allow for genotyping
PCR	Rapid addition of new viruses Detection of unidentified respiratory viruses Suitable for early detection and monitoring of viruses	Highly sensitive but sometimes false products Containment of amplicons to prevent contamination
Real Time PCR	Rapid product confirmation High Sensitivity and Specificity Automated	Limited number of virus detection in one-tube False signal High cost
Microarrays	Rapid Can screen multiple pathogens	Low sensitivity False signal

Table 4. Methods Used For Laboratory Diagnosis of RSV

4. Conclusion

Lower respiratory tract infections caused by RSV occur epidemically, and the appearance of epidemics seems to vary with latitude, altitude and climate. Onset weeks and durations of RSV seasons also vary substantially by year and location. Local RSV data are needed to accurately define the onset and offset of RSV seasons and to refine timing of passive immune prophylaxis therapy recommendations. Further studies on RSV particularly in developing countries should address these questions in more detail. RSV is an important pathogen of young children in tropical and developing countries and a frequent cause of hospital admission. Prevention of RSV disease relies on rapid diagnosis, infection control and hygiene measures, as well as providing immunoprophylaxis in select infants. The prophylaxis, however, is costly, and so targeting the recipient population and timing of administration is important for optimal effectiveness and judicious use of limited health care resources

The relative proportions of different genotypes vary from year to year with steady replacement of the dominant genotype each year, suggesting that herd immunity may play a role in the abundance of a particular genotype in a particular epidemic. A small study in Hungary (Pankovics et al., 2009) using molecular detection and genetic analysis showed that based upon the F region 96% viruses genetically belonged to type A and 4% were classified as type B human RSV. Based upon the G region, out of the type A viruses 72.7% belonged to group GA5 and 27.3% to group GA2. Viral nucleotide sequence was identical in several cases. A Japanese study (Shobugawa et al., 2009) investigated a total of 488 human RSV samples from 1,103 screened cases in a pediatric clinic in Niigata. According to the phylogenetic analysis, among the PCR-positive samples, 338 HRSV-A strains clustered into the previously reported genotypes GA5 and GA7 and two novel genotypes, NA1 and NA2, which were genetically close to GA2 strains. Another study In India (Agrawal et al., 2009) showed that 95% were group B strains and 5% group A. Similarly, an outbreak in Turkey indicated that subgroup B was highly dominant (Guney et al., 2004). In Thailand, equal infectivity and severity of both RSV subgroups has been shown (Boonyasuppayakom et al., 2007). Such knowledge has yet to be ascertained for the Middle Eastern countries. There is a dustinct need to carry out molecular typing of RSV in Saudi Arabia and other surrounding countries to further elucidate the pattern of infections, the prevalent strains circulating in the region and possible approaches for treatment. The importance of RSV infections has resulted in surveillance monitoring being conducted in Europe and other developed countries. Such coordinated strategies are important to consider in developing countries where the impact of RSV infections is greater.

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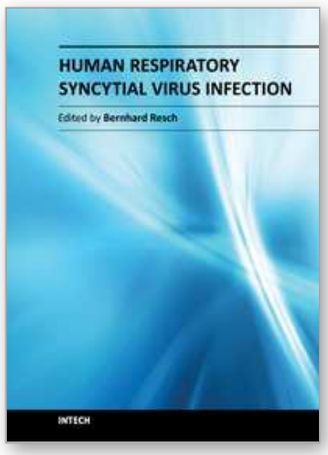

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In this online Open Access book on "Human RSV Infections", several distinguished authors contribute their experience in respiratory syncytial virology. A major focus lies on the fascinating pathophysiology of RSV and represents recent and actual work on different mechanisms involved in the complex pathogenesis of the virus. The second section elucidates epidemiologic and diagnostic aspects of RSV infection covering a more clinical view of RSV disease. At last, treatment modalities including the search for a vaccine that is still not in sight are discussed and conclude this book, thus building up a circle that runs from experimental models of RSV related lung disease over clinical aspects of disease to the latest news of therapeutic and prophylactic approaches to human RSV infection.

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