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Research Article

# Virologic Profile of Acute Respiratory Infections in Children by FilmArray Multiplex PCR: A Prospective Observational Study in a Hospital Setting in Casablanca, Morocco

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## Abstract

**Background:** Acute Lower Respiratory Infections are a heavy burden on the Heath system. The viral cause is the most prevalent in children. The techniques of detection by molecular biology have made it possible to broaden the virological diagnosis and to optimize the therapeutic management. The aim of our work is to describe the epidemiological and virological characteristics of our patients and to specify the factors associated with the severity of the disease by evaluating the need for oxygen and the duration of hospitalization in the patients. **Patients and Methods**: this is a cross-sectional prospective study carried out from January 1 to February 28, 2021 in the pediatrics department at Cheikh Khalifa Hospital in Casablanca. The epidemiological, clinical and paraclinical data of the patients were collected on an admission form. The virological diagnosis was carried out on nasopharyngeal swabs by the multiplex Polymerase Chain Reaction (PCR) test. **Results:** A total of 85 cases were included with a median age of 9 months. Children under 12 months of age accounted for 55.3% of cases. The predominant clinical picture was wheezing dyspnea (45.9%). The median length of hospital stay was 5 days [3 - 6]. RSV, rhinovirus, influenza A and H1N1 influenza are detected in 50.8%, 17.5%, 17.5% and 5.2% respectively. Co-infection with 2 viruses is noted in 3 cases. By comparing the patients who required oxygen therapy with those who did not have this need, a statistically significant difference according to age ($p < 0.001$), length of stay ($p = 0.019$), CRP level ($p = 0.02$) and whether or not the chest x-ray was pathological ($p = 0.005$) was found. **Conclusion:** This study made it possible to determine the virological agents most implicated in ARI during the winter period in our patients. The multiplex PCR detection technique, although expensive, is rapid and efficient. Its routine use should reduce the number of unnecessary paraclinical examinations and the overuse of antibiotics.

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**Keywords**: Acute respiratory infection; Child; Virus; Multiplex PCR

## Introduction

Acute respiratory infections (ARI) in children represent a major public health issue given their high prevalence, severity, and the health costs they generate. In Morocco, as in developing countries, acute lower respiratory infections represent a major cause of morbidity and mortality, especially in children under 5 years old. In its 2015 report, the Ministry of Health estimated that 32,251 children under 59 months presented a serious respiratory pathology during the year 2014 in the different regions of Morocco [1]. Across the world, the annual prevalence of acute respiratory infections in a healthy 3-year-old is about three to 10 infections per year [2]. Viruses are the infectious agents mainly involved in the initial symptomatology of ARI in children [3,4]. Human rhinovirus is the most common virus universally across all age groups, while Respiratory Syncitial Virus (RSV) is dominant in infants according to several studies [5]. Viral agents are responsible for upper respiratory infections (laryngitis or tracheitis) but also lower respiratory infections (bronchitis, bronchiolitis, pneumopathy) that are potentially more serious. Clinical symptoms specific to the pathogen, whether viral or bacterial, are often lacking.

The development of new techniques aimed at determining the exact epidemiological profile of these infections will allow them to be better controlled and a rationalization of the excessive prescription of antibiotics. Compared to immunohistochemistry and conventional cultures, Polymerase Chain Reaction (PCR) techniques reveal a much wider viral spectrum, including already known organisms, but also so-called "emerging" viruses such as COVID19 most often from genetic recombination [6]. Multiplex PCR is a highly sensitive and highly specific molecular test for the detection of viral nucleic acids in respiratory secretions [7]. According to a meta-analysis including seven studies done in developed countries and two in developing countries, the molecular diagnosis of the viral origin of respiratory infections in children was recorded in 49% of case (range 43-67%) [8]. For this highly sensitive but qualitative detectability to be used optimally in the diagnostic evaluation of affected children, primary viral infections must be distinguished from secondary bacterial infections through other paraclinical tools. Considering the cost which remains high of this technique, its profitability on the medical and economic plan is still to be dismantled [7].

The multiplex PCR platform recently available in Morocco allows multiple molecular analysis in a very short time and often makes it possible to distinguish between viral and bacterial infections, thus promoting the implementation of a therapeutic strategy targeted on the responsible pathogen. The documentation of the type of viral infection by PCR and the clinical, radio-biological and evolutionary characteristics of the patients are examined in our study. An analysis of the factors associated with the severity of the disease by evaluating the need for oxygen and the length of hospital stay in our patients is performed.

In Morocco, studies on the molecular detection of viral etiologies of ARI are rare. The aim of this study is to determine the prevalence rate of the predominant viral strains responsible for respiratory infections in our region and to compare our results with published data. Thus, knowledge of our viral ecosystem can inform seasonal epidemiological surveillance and guide our patient care.

### Patients and methods

This is a prospective and descriptive study, conducted at the Cheikh Khalifa Ibn Zaid University Hospital in Casablanca. Eighty-five children under 15 hospitalized for ARI during a 2-month period (January 1 to February 28, 2021) were included in the study.

The children enrolled in the study had a clinical picture of acute upper (laryngitis) or lower (bronchiolitis or pneumonia) respiratory infections which developed a few days before admission to hospital. We included in the study any child under 15 years hospitalized for ARI (acute respiratory distress, moderate or severe viral bronchiolitis, moderate or severe febrile asthma attack, clinical picture of pneumonia or symptomatology suggesting whooping cough) who received a nasopharyngeal swab after parental consent (given the financial cost of this analysis).

The adolescents over 15 years of age and children hospitalized for a non-respiratory medical condition or a surgical cause were excluded. At hospital registration, an already established questionnaire is completed for each patient hospitalized for ARI. Demographic (age, sex, place of accommodation, etc.), clinical, radiological and biological characteristics were collected. Nasopharyngeal aspirations were performed upon hospitalization, stored at 4 to 8 ° C and sent within 4 hours of collection to the National Reference Laboratory (NRL) of the hospital. The samples were analyzed in the laboratory by multiplex real-time PCR with the FilmArray® respiratory panel kits. This panel can detect 17 Viruses and 3 bacteria (Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae).

Written informed consent was obtained from the parents or legal guardians of each child.

Data were coded and entered using Jamovi statistical software version 1.6.23. Data were summarized using the mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies and percentages for categorical or qualitative variables. To facilitate comparability

with other studies already published, children have been classified into two age groups: a group with infants (aged less than one year) and a 2nd group with infants (aged over 1 year) and children up to 15 years. Most of the results are transformed into qualitative variables for comparison by chi-square test or Fisher's exact test in case of insufficient theoretical numbers. Association analysis between certain parameters is measured by Spearman's correlation analysis. The significance level was set at 5% and p values less than 0.05 are considered statistically significant.

## Results

A total of eighty-five cases validated the inclusion criteria and were included in the study. Almost all the cases (92%) were residents of the Casablanca / Settat region. The sex ratio is 1.74 (M/F). Hospitalized children are aged 1 month to 15 years with a median age of 9 months. Children under one year old represent 55.3% (47/85). The epidemiological, clinical and para-clinical characteristics of the study patients are presented in 9 (Table 1) The main clinical manifestations observed on admission included wheezing dyspnea in 45.9%, febrile respiratory distress in 35.3%, febrile asthma attack in 15.3% and pertussis cough in 3.5%. The median length of hospital stay is 5 days [3 - 6]. There was a significant difference between the frequency of certain respiratory pathologies according to age (Khi2 p <0.001). Hospitalizations for wheezing dyspnea for viral bronchiolitis (p <0.001) were statistically significantly more frequent in infants.

| **Characteristics** | **Population = N (%)** |
|---|---|
| **Median age*** | 9 months [3 – 23] |
| Age less than a year | 47 (55,3%) |
| Age over a year | 38 (44,7%) |
| **Gender**: Male | 54 (63,5) |
| **Duration of hospitalization*** | 5 days [3 – 6] |
| **Reason of hospitalization** | |
| Wheezing dyspnea | 39 (45,9%) |
| Febrile respiratory distress | 30 (35,3%) |
| Febrile asthma attack | 13 (15,3%) |
| Whooping cough | 3 (3,5%) |
| **Underlying land** | |
| Atopy | 13 (15,3%) |
| Heart disease | 6 (7,1%) |
| **CRP:** | |
| Negative | 54 (63,5%) |
| Positive | 31 (36,5%) |
| **Chest x-ray** | |
| Normal | 38 (44,7%) |
| Pathological | 47 (55,3%) |
| **Hospital Care** | |
| Antibiotic therapy | 47 (55,3%) |
| Corticosteroid therapy | 12 (14,1%) |
| **Evolution** | |
| Favorable | 80 (94%) |
| Unfavorable | 5 (6%) |

**Table 1**: Epidemiological, clinical and paraclinical characteristics of the patients; *Expressed as median and quartiles; CRP: C-Reactive Protein.

Regarding the viral study of the nasal swab by multiplex PCR, 57 cases (67%) had a positive sample with isolation of a Respiratory Syncytial Virus (RSV) in 50.8% (29 cases) (Table 2). Rhinovirus represented 17.5% (10 cases), influenza A had a rate of 17.5% (10 cases) and H1N1 influenza at 5.2% (3 cases). A single case of pertussis was identified while no atypical bacterial germs were found (Table 2).

| Types of viruses | Numbers and percentages N (%) |
|---|---|
| PCR negative | 28 (33) |
| PCR positive : | 57 (67) |
| • VRS* | 29 (50) |
| • Rhinovirus | 10 (17,5) |
| • Influenza A<br>• H1N1 flu<br>• Influenza B | 10 (17,5)<br>03 (5,2)<br>01 (1,75) |
| • Métapneumovirus | 01 (1,75) |
| • Adenovirus | 01 (1,75) |
| • Coronavirus NL63 | 01 (1,75) |
| • Bordetella Pertussis (Whooping cough) | 01 (1,75) |

**Table 2**: Viral etiologies detected by multiplex PCR; RSV: Respiratory Syncytial Virus.

The comparison between the two groups of patients who required or not the use of oxygen therapy during hospitalization showed a statistically significant difference as a function of age (Khi2 p <0.001), length of stay (Khi2, p = 0.019), the CRP level (Khi2, p = 0.02), whether the chest radiograph is pathological (Khi2, p = 0.005) and the use of corticosteroid therapy (Khi2, p = 0.026) (Table 3). There is also a correlation between the need for oxygen and the length of hospital stay (Spearman's p at 0.019 with an r at - 0.25). There is no statistically significant difference between the children requiring oxygen and those who do not require it concerning the sex (Khi2, = 0.632), the presence or not of RSV in the nasal PCR (p 0.198) and the use or not of antibiotic therapy (Khi2, p = 0.057). There was no significant difference between virus type and length of hospital stay (Ficher's exact Test = 0.180) (Table 3).

| Factors studied | Oxygen requirement Yes (N= 33) | Oxygen requirement No (N=52) | P |
|---|---|---|---|
| **Age :** | | | |
| Less than 1 year | 37,6 | 17,6 | **P <0,001** |
| Greater than 1 year | 1,2 | 43,6 | |
| **Gender :** | | | |
| F | 13 | 23,6 | P = 0,632 |
| M | 25,8 | 37,6 | |
| **Duration of stay :** | | | |
| Short | 35,4 | 42,3 | **P = 0,019** |
| Long | 3,5 | 18,8 | |

| | | | |
|---|---|---|---|
| **Asthma :** | | | |
| No | 37,6 | 47,1 | **P = 0,012** |
| Yes | 1,2 | 14,1 | |
| **CRP level:** | | | |
| **Negative** | 30,5 | 32,9 | **P = 0,020** |
| **Positive** | 8,2 | 28,4 | |
| **Chest x-ray:** | | | |
| Normal | 24,7 | 20 | **P = 0,005** |
| Pathological | 14,2 | 41,1 | |
| **Nasopharyngeal PCR:** | | | |
| Absence of RSV | 22,4 | 43,5 | P = 0,198 |
| Presence of RSV | 16,5 | 17,6 | |
| **Antibiotic therapy:** | | | |
| No | 22,3 | 22,3 | P = 0,057 |
| Yes | 16,5 | 38,9 | |
| **Corticosteroid :** | | | |
| **No** | 36,6 | 45,8 | **P = 0,026** |
| **Yes** | 2,3 | 15,3 | |

**Table 3**: Factors Associated with the Need for Oxygen in Inpatients with ARI; CRP: C-Reactive Protein; PCR: Polymerase Chain Reaction; RSV: Respiratory Syncytial Virus.

## Discussion

Our study is among the first in Morocco to focus on analyzing the viral molecular epidemiology of our patients with ARI through multiplex viral PCR. We noted a male predominance and the age group below 12 months. RSV is the most common virus found on viral analysis. Factors associated with disease severity when studying oxygen requirement are represented by age, length of stay, presence of asthma, CRP level, radiological abnormalities, and prescription of corticosteroid and antibiotic therapy.

Virological diagnosis by the multiplex PCR technique has found all its interest in refining the epidemiological data by demonstrating a wide viral spectrum in a very short time. The FilmArray Respiratory Panel (FA-RP), used by our laboratory, is a multiplex PCR certified by the FDA (Food and Drug Administration) that detects 17 viruses and 3 bacteria responsible for upper respiratory tract infections. It does not require sophisticated equipment or molecular diagnostic expertise, so it is a valuable tool for assessing the age-related prevalence of these pathogens [9]. In addition to its high cost, the main limitation of this technique is that it cannot decide whether the infection is active or old. The presence of nucleic acids belonging to the virus can be found for a prolonged period, and therefore positive for PCR several weeks after an infection (5 to 6 weeks after a rhinovirus infection) [10]. The result is only qualitative, which should encourage a careful interpretation of the results and the implication of the infectious agent in respiratory infection, especially in the event of co-detection of several viruses or strong suspicion of bacterial superinfection.

In our study, we identified 85 cases of ARI who received a nasal swab over a 2-month winter period. The reasons for hospitalization for respiratory pathology were largely dominated by wheezing dyspnea in the context of viral bronchiolitis

(45.9%), whereas this represents 24.4% in the Moroccan study by Benchekroun et al [1]. Asthma exacerbations are noted in us in 15.3% while in the study by Benchekroun et al was 51.1% [1]. Patients under 12 months of age represented 55.3% of our study population, which explains the predominance of viral bronchiolitis. The percentage of infants under 12 months also occupied 47.6% in the study by Bangui et al and 48.1% in the study by Benchekroun et al [11,1]. There was a sex ratio of 1.74 with an estimated male predominance of 63.5%. A similar result was found in the study by Benchekroun et al and Hattoufi et al in Morocco, Evenou et al in France and Hatipoglut et al in Turkey [1,12,13].

The rhinovirus is the most common viral microorganism across all age groups, while RSV, this regular and highly contagious winter visitor, is more prevalent in infants [14]. Rhinovirus infection is predominant with a rate of 47.5% in the Bangui et al series and 69.8% in the Lebanese series [11,4]. However, RSV dominates in studies from Niger, Jordan, Morocco, Turkey and India [6,7,13,15]. This predominance of RSV in infants suggests that maternal antibodies are ineffective in preventing RSV infections during infancy [15]. In our study, RSV was isolated in 50.8% of cases, while rhinovirus only occupied 17.5% of positive samples.

The multiplex PCR technique has become a major advance in the diagnosis of multiple viral co-infections, reaching very high levels of sensitivity and specificity of around 95% [16]. The simultaneous detection of several viruses in pediatric patients varies in studies between 10 and 30% [17] while our study found only 3.5% of co-infections. Recent systematic reviews and meta-analyzes concluded that there was no significant difference between co-infection and severity of respiratory disease [17]. While others have concluded to the contrary, testifying that other factors play a role in the severity of ARIs in addition to co-infection [18,19].

More than half of our cases had a viral ARI as evidenced; CRP, a reliable marker of bacterial infection, which is negative in 63.5%; and detection of a virus by PCR, which is noted in 67% of cases. However, the use of antibiotics was indicated in 55.5% with clinical arguments and radiobiological abnormalities. Some experts recommend that all patients with true pneumonia should be given antibiotics because excluding the presence of associated bacterial infection is not possible [8]. The recommendations of the British Thoracic Society are that antibiotic treatment can be stopped in children with mild illness, possibly viral [20]. Such a decision is difficult to take in front of a critically unstable child.

Due to ethical concerns, only one randomized, placebo-controlled study has been performed in children to investigate the need for antibiotic treatment in community-acquired pneumonia [21]. In 136 children, RSV was detected in 84% of cases and no clinically significant efficacy of antibiotics was recorded [21]. So, decreasing the use of unnecessary antibiotics is the key to tackling antibiotic resistance. According to Shiley et al, one hypothesis that could explain the use of antibiotics after a positive viral molecular diagnosis is the clinician's anxiety about the possibility of a concomitant bacterial ARI or superinfection [22].

The use of antivirals in the treatment of severe pneumonia or in immunocompromised conditions is increasingly carried out [8]. Neuraminidase inhibitors, such as oseltamivir and zanamivir, were developed in the 1990s and have played a well-established role in the early treatment of severe influenza A and B infections [23,24]. No cases received antivirals in our study. The use of corticosteroids for the treatment of community-acquired viral pneumonia is controversial and may vary depending on the virus involved and the severity of the symptoms. Their ineffectiveness in the treatment of respiratory syncytial virus infections is well established [25].

Severe forms accompanied by desaturation require, in addition to the treatment initiated, oxygen therapy [25]. In our study, the comparison between the two groups of children who required or not oxygen therapy during hospitalization showed a statistically significant difference according to age, length of stay, presence of asthma, the CRP level and depending on whether or not the chest x-ray is pathological. The oxygen requirement in our patients was necessary in 38.8% of all ages, including 97% in those under one year old. Children with high CRP or pathological x-rays had higher oxygen requirements. There was no statistically significant difference between virus type and length of hospital stay. The same result was proven by Megly et al in an Egyptian study [26].

For the preventive arm of viral ARIs, the influenza vaccine or other new viral vaccines have shown great efficacy [27]. Low incidence seasons may represent a target window for vaccination so that the antiviral immunity of the population can be maximized before the onset of the influenza season, and the morbidity and mortality associated with viral infection can be minimized [28]. On the other hand, the high seasonal detection rate of a virus may indicate a future epidemic and therefore a serious threat to public health, which justifies a rigorous surveillance system to allow rapid preparation and management and effective [29]. Like much of the published work, ambulatory and mild cases were not included in our study, which could affect the integrity of the pathogen profile found.

## Conclusion

This study makes it possible to educate our doctors on the importance of an appropriate etiologic diagnosis of the ARI of the child in order to know our own viral ecosystem. The results of our study agree with most of the publications on the viral predominance

of ARI and on the preponderance of RSV in small infants. These results can provide an important reference for further local and multicenter research by widely evaluating the medico-economic impact on our practices in order to justify the place of these expensive multiplex tests in the management of patients, in terms of reduction of the length of hospitalization, over-prescription of antibiotics and laboratory and radiological examinations.

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