ORIGINAL ARTICLE

Viral respiratory infections (excluding SARS-CoV-2) in Morocco : A retrospective study from September 2019 to April 2023

Les Infections respiratoires virales (à l'exclusion du SARS-CoV-2) au Maroc : une étude rétrospective de septembre 2019 à avril 2023

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Abstract

Introduction : Viral respiratory infections are a significant cause of morbidity and mortality worldwide. Viruses are implicated in more than 80% of respiratory infections.

Objectives: The aim of this work was to study the epidemiology of respiratory viruses and assess the impact of the COVID-19 pandemic on their circulation between 2019 and 2023.

Materials and methods : This retro-prospective descriptive study was conducted at the Virology Laboratory of the Mohammed V Military Teaching Hospital in Rabat, Morocco from September 2019 to April 2023. Samples were collected from patients admitted with acute respiratory infection that tested negative for SARS-CoV-2 by PCR and underwent multiplex respiratory PCR test using the BioFire® Respiratory 2.1 kit on a nasopharyngeal swab. Demographic data were extracted from Laboratory Information System. Statistical analysis was carried out using SPSS 22.0 and Microsoft Excel.

Results: A total of 1050 PCR tests were performed. The positivity rate was 54% (564 patients). The median age of patients with a positive PCR was 31 years (1-91 years). The M/F sex ratio was 1.52. The positivity rate was 57%, 53%, 72%, 52% and 44% during the years 2019 (September to December), 2020, 2021, 2022 and 2023 (January to April) respectively. Among the viruses detected, Enterovirus/Rhinovirus was the most common (50%), followed by Influenza virus (16%) and Respiratory Syncytial Virus (11%). Four hundred fifty positive PCRs was mono-infections (80%) and 114 (20%) were co-infections, of which 108 were with 2 viruses and 6 with 3 viruses.

Conclusion : The implementation and lifting of pandemic-related barrier measures significantly influenced respiratory virus circulation, aligning with seasonal patterns. In our context, Enterovirus/Rhinovirus and Influenza testing is recommended first for adults whereas Enterovirus/Rhinovirus and RSV testing is recommended first for children. Otherwise, multiplex testing should be considered for severe cases or those with risk factors.

Keywords : Respiratory viruses, Multiplex PCR, Epidemiology, Morocco

Résumé

Introduction : Les infections respiratoires virales sont une cause majeure de morbidité et de mortalité dans le monde. Les virus sont impliqués dans plus de 80 % des infections respiratoires. Objectifs : L'objectif de cette étude était d'analyser l'épidémiologie des virus respiratoires et d'évaluer l'impact de la pandémie de COVID-19 sur leur circulation entre 2019 et 2023.

Matériels et méthodes : Cette étude descriptive rétrospective et prospective a été menée au Laboratoire de Virologie de l'Hôpital Militaire d'Instruction Mohammed V à Rabat, au Maroc, de septembre 2019 à avril 2023. Les échantillons ont été prélevés chez des patients hospitalisés pour infection respiratoire aiguë, dont le test PCR SARS-CoV-2 était négatif, et ont subi un test PCR multiplex respiratoire à l'aide du kit BioFire® Respiratory 2.1 sur un prélèvement nasopharyngé. Les données démographiques ont été extraites du système d'information du laboratoire. L'analyse statistique a été réalisée avec SPSS 22.0 et Microsoft Excel.

Résultats : Un total de 1 050 tests PCR a été effectué. Le taux de positivité était de 54 % (564 patients). L'âge médian des patients avec un test PCR positif était de 31 ans (1-91 ans). Le ratio homme/femme était de 1,52. Les taux de positivité étaient respectivement de 57 %, 53 %, 72 %, 52 % et 44 % au cours des années 2019 (septembre à décembre), 2020, 2021, 2022 et 2023 (janvier à avril). Parmi les virus détectés, l'Enterovirus/Rhinovirus était le plus fréquent (50 %), suivi du virus Influenza (16 %) et du virus respiratoire syncytial (11 %). Quatre cent cinquante PCR positifs correspondaient à des mono-infections (80 %), tandis que 114 (20 %) étaient des co-infections, dont 108 impliquant deux virus et 6 impliquant trois virus.

Conclusion : La mise en place et la levée des mesures barrières liées à la pandémie ont significativement influencé la circulation des virus respiratoires, en accord avec les schémas saisonniers. Dans notre contexte, le dépistage de l'Enterovirus/Rhinovirus et de la grippe est recommandé en priorité chez les adultes, tandis que celui de l'Enterovirus/Rhinovirus et du VRS est recommandé en premier chez les enfants. Par ailleurs, le test multiplex devrait être envisagé pour les cas sévères ou présentant des facteurs de risque.

Mots clés : Virus respiratoires, PCR Multiplex, Epidémiologie, Maroc

INTRODUCTION

Respiratory viral infections are a major cause of morbidity and mortality worldwide. Respiratory viruses are implicated in over 80% of all respiratory infections, making them the leading cause of community and nosocomial epidemics. There are a considerable number of viruses with a primary respiratory tropism, some of which have long been known, such as Influenza virus, Respiratory Syncytial Virus (RSV), Enterovirus/ Rhinovirus, etc., while others such as Metapneumovirus and Bocavirus have been incriminated more recently. In addition, new respiratory viruses regularly emerge in humans, with a global pandemic risk (e.g. pandemic Influenza viruses, SARS-CoV, MERS-CoV and SARS-CoV-2) (1).

Diagnostic methods for respiratory viruses, in particular molecular tests such as multiplex PCR, have advanced considerably in recent years. These tests can detect multiple pathogens simultaneously optimizing patient management and facilitating epidemiological surveillance of respiratory viruses, particularly during the COVID-19 pandemic (2). It is therefore important to study possible changes in the ecosystem of respiratory viruses following the emergence of SARS-CoV-2, as well as the impact of various preventive measures undertaken to reduce the spread of SARS-CoV-2, on the incidence of other respiratory viruses (3). The aim of this study was to investigate the epidemiology of respiratory viruses (excluding SARS-CoV-2) at the Mohammed V Military Teaching Hospital between September 2019 and April 2023, and to analyze the infections prevalence before, during and after the COVID-19 pandemic.

MATERIALS AND METHODS

Type, location and period of study

This was a descriptive retrospective study conducted at the Virology Laboratory, Center of Virology and Infectious and Tropical Diseases at the Mohammed V Military Teaching Hospital (Rabat), spanning a period of 44 months (from September 2019 to April 2023).

The study enrolled patients exhibiting symptoms of acute respiratory infections, based on the National Institute for Health and Care Excellence (NICE) criteria (1). These included a sudden onset of fever and cough, accompanied by one or more of the following: fatigue, headache, muscle pain, sore throat, nasal congestion, shortness of breath, loss of appetite, nausea, vomiting, or diarrhea. Patients who met the World Health Organization (WHO) case definition of severe acute respiratory illness (SARI) were also included (3); defined as acute respiratory failure with a history of fever exceeding 38°C, cough, symptoms onset within the past 10 days and requiring hospitalization. Patients with a positive SARS-CoV-2 PCR (Eurobioplex SARS-COV-2 multiplex Kit) and patient with bacterial infections were excluded.

Methods

Nasopharyngeal swabs were collected using a swab kit and transported in an appropriate medium, such as Biocomma® or Copan®. Virus detection was performed using a multiplex respiratory panel, FilmArray RP 2.1 plus BioFire multiplex respiratory panel. This panel allows simultaneous detection of viruses and bacteria in less than one hour (1). The principle of the reaction is based on nested PCR with melting curve analysis. The cassettes were prepared by injecting 1ml of the hydration solution and 300µl of the sample combined with its buffer. Then, the cassette is placed in the FilmArray system and the analysis program is started. It is a unitary, closed, disposable system that contains all the chemical reagents necessary to isolate, amplify, and detect nucleic acids of multiple respiratory viruses and bacteria in a single sample. The list of pathogens detectable by this panel includes 19 viruses: Adenovirus (ADV), Coronavirus 229E (CoV 229E), Coronavirus HKU1 (CoV HKU1), Coronavirus NL63 (CoV NL63), Coronavirus OC43 (CoV OC43), MERS-CoV, SARS-CoV-2, Metapneumovirus (hMPV), Infuenza A Virus (IAV), Infuenza A/H1, Infuenza A/H1-2009, Infuenza A/H3, Infuenza B virus (IBV), parainfuenza viruses 1 to 4 (PIV1-4), Human Enterovirus/Rhinovirus, respiratory syncytial virus (RSV), and 4 bacteria (*Bordetella pertussis, Bordetella parapertussis Mycoplasma pneumoniae, and Chlamydophylla pneumoniae*). Accordingly, when the internal control fails, the software generates an «invalid» result for all pathogens in the panel.

Data collection and statistical analysis

Patient demographic data were extracted from the laboratory information system. Data was collected on a Microsoft EXCEL file. Statistical analysis was carried out using Microsoft Excel and SPSS version 21 software (SPSS Inc., Chicago, III, USA). The difference between the ratios was evaluated using the chi-square test and Fisher's exact test. A p-value below 0.05 was considered statistically significant.

Ethics committee

According to Moroccan law 28-13 on the Protection of Individuals Involved in Biomedical Research, this protocol is classified as a non-interventional study, which exempts it from requiring ethical committee or IRB approval. This exemption is in accordance with **Dahir n° 1-15-110 of 18 Chaoual 1436 (4 August 2015)**, which promulgated **Law n° 28-13** concerning the protection of individuals participating in biomedical research. (https://www.sante.gov.ma/Reglementation/REGLEMENTATIONDESPRATIQUESMEDICALES/28-13.pdf).

Written informed consent was carefully obtained from all participants (or from family for intensive care unit patients) ensuring compliance with ethical standards.

RESULTS

Between September 2019 and April 2023, a total of 1050 respiratory PCR tests were performed. The number of respiratory multiplex PCR tests performed in the last trimester of 2019 was 21. In 2020, this number amounted to 103 tests, while it increased to 169, 463 and 294 tests in 2021, 2022 and 2023 (January to April) respectively (Figure 1).

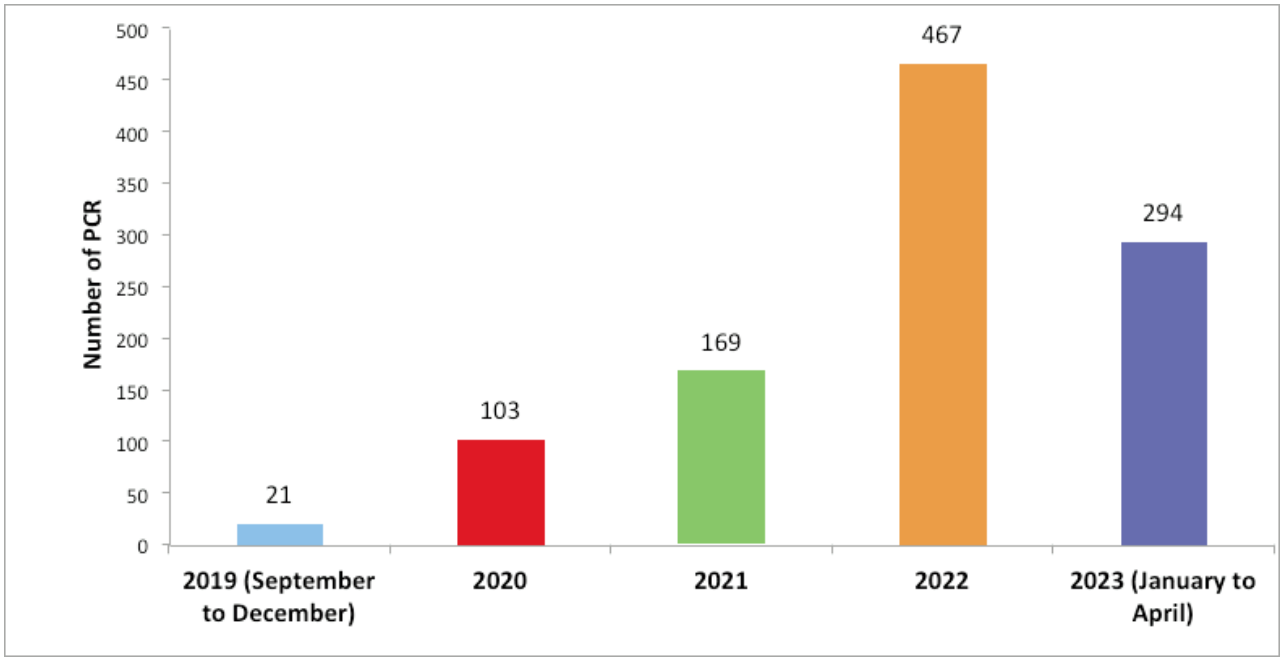

Figure 1 : Distribution of multiplex PCR tests during the study period (N=1050)

During the study period, 564 of the 1,050 samples were positive, giving an overall positivity rate of 54%. The highest positivity rate per year was observed in 2021 (72%, 122 positive samples out of 169 samples collected in 2021), followed by 2022 (52%, 244 positive samples out of 463 samples collected in 2022) and 2020 (53%, 55 positive samples out of 103 samples collected in 2020) ($p > 0,05$). It should be noted that we detected 12 viral infection from September to December 2019 and 294 from January to April 2023.

Of the 564 positive samples, only 262 samples were received with age information; ages ranged from 1 day to 91 years, with an average age of 31 years. Adults (> 15 years) accounted for 153 (58%). In the 0-5 age group, 103 (39%) samples were positive. In contrast, children aged 5 to 15 accounted for only 6 cases of the 262 positive samples with known age information. Of all positive samples, male patients predominated with 341 (60%). Thus, the M/F sex ratio was 1.52.

Among the various prescribing departments, the highest positivity rate was observed in the pediatric department, with a total of 168 (29%) positive cases of total positive cases, followed by the clinical hematology department with 50 (8%) positive cases, then the infectious diseases department and the pediatric intensive care unit with 42 (7%) and 41 (7%) positive cases respectively ($p < 0,05$). In outpatients, 171 viral infections were detected (Figure 2).

In 2020, the positivity rate was highest in winter (78%, 42 cases were detected in winter of the whole 55 positive cases detected this year), no positive cases were detected in spring, only 4 positive cases were detected in summer and finally 9 cases were detected in autumn ($p < 0,05$). Circulation picking up in 2021 especially in spring (33%, 41 of the 122 positive samples in 2021) and autumn (37%, 46 of the 122 positive samples in 2021), then autumn 2022 (36%, 88 of the 244 positive samples in 2022) and winter 2022 (28%, 68 of the 244 positive samples in 2022) (Figure 3).

In term of seasonality, incidence of viruses was highest during the winter season (248 viruses detected, 44%), followed by autumn (155, 27%), spring (106, 18%) and summer (55, 9%) ($p < 0.05$). However, for the year 2021 and 2022, viruses were more frequently found in autumn (46 and 88 positive samples respectively). In 2023, autumn prevalence was not evaluated as it fell outside the study period.

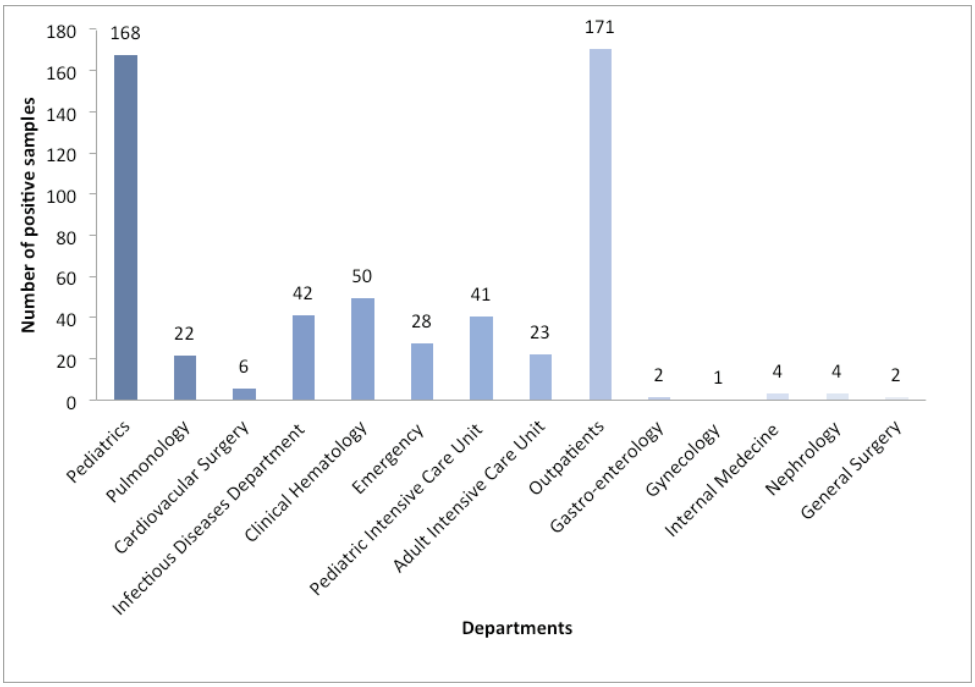

Figure 2 : Distribution of positive samples by departments (N=564)

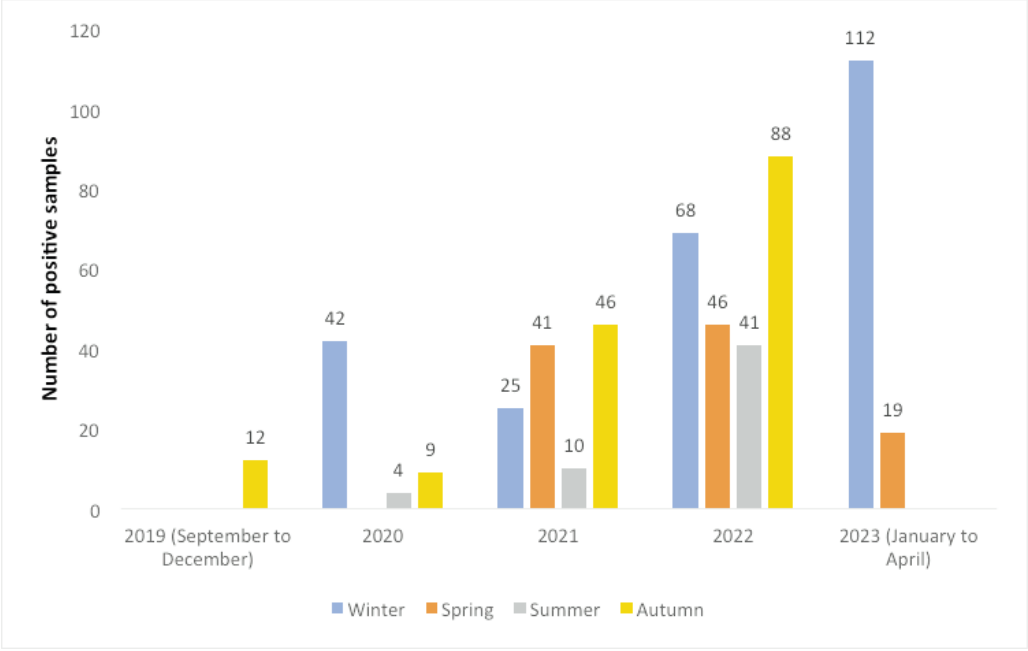

Figure 3 : Number of positive samples according to the seasons (N=564)

Enterovirus/Rhinovirus mono-infection was predominant in all departments, it was found in 50% (281 of 564 positive samples). In adults, Enterovirus/Rhinovirus mono-infection was detected in 75 cases of the 153 positive adults (49%), followed by Influenza A (13%). In children aged 0 to 5, Enterovirus/Rhinovirus mono-infection was detected in 51 cases of the 103 positive children (49%), followed by RSV (17%). Among children aged 5 to 15, Enterovirus/Rhinovirus mono-infection was identified in 3 out of 6 positive cases (50%), while influenza A virus, RSV, and adenovirus were each detected in one case (Fig. 4 a, b and c).

Despite uninterrupted circulation of the Enterovirus/Rhinovirus, the evolution of Enterovirus/Rhinovirus is characterized by seasonal peaks, mainly in autumn and winter. Summer generally appears to be a period of low virus circulation, with the notable exception of 2022. During the study period, Influenza, RSV, Metapneumovirus and Adenovirus exhibited limited circulation from 2019 through the end of 2021. Starting in

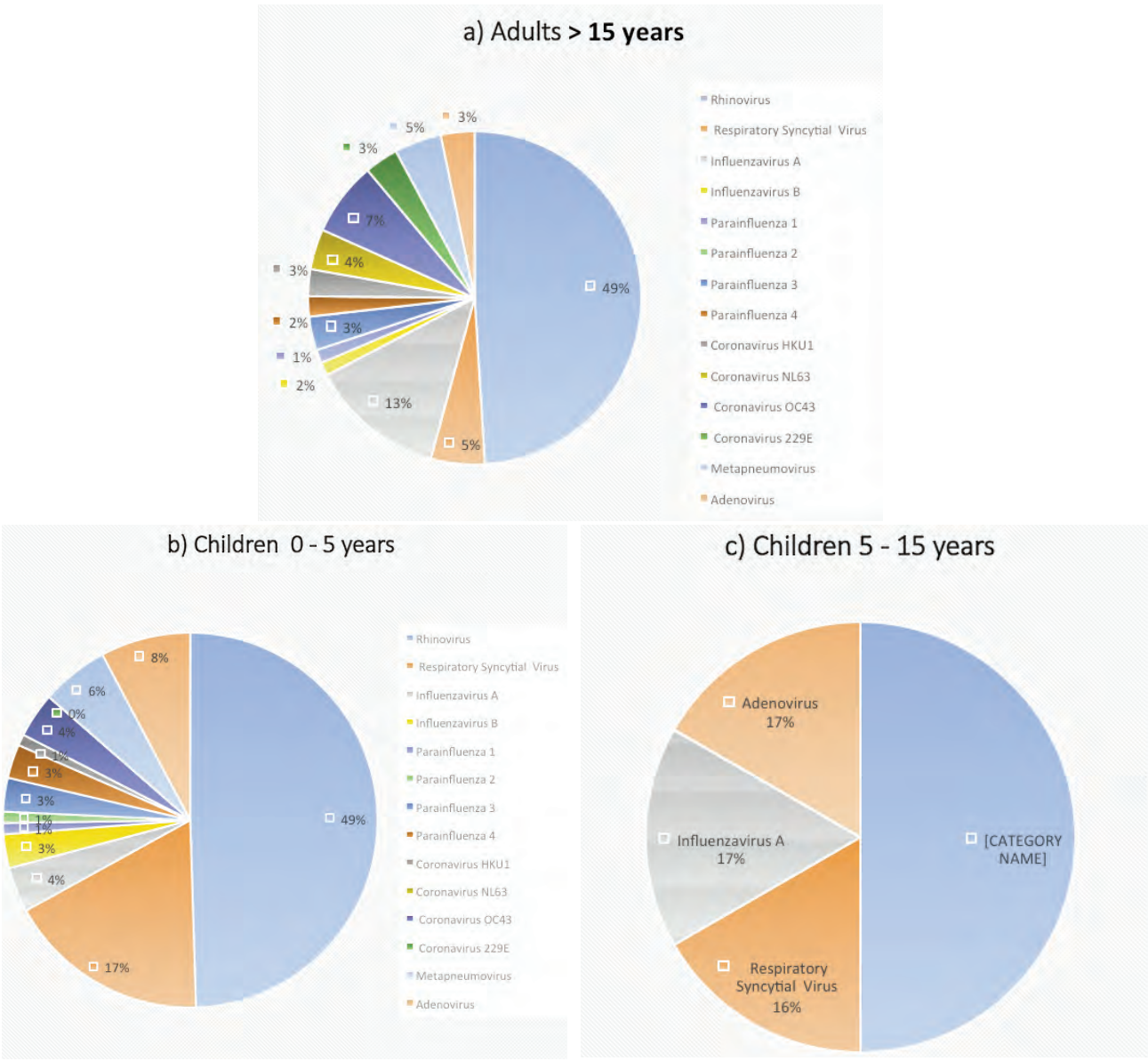

Figure 4 : Distribution of detected viruses by age group (N=262), a)adults >15 years, b) children 0-5 years, c) children 5-15 years

autumn 2021, we diagnosed an increasing number of Influenza, RSV and Adenovirus cases, particularly during the autumn and winter seasons of 2022 and 2023. The main trend for RSV remains a predominant circulation during autumn and winter. However, the 2022 data show spring and summer circulation of RSV. Classical coronavirus were detected mainly in winter. Para-Influenza virus type 3 was common in winter 2020, then in spring 2021, and again in autumn 2022 and 2023, Para-Influenza virus type 1 was not detected in 2019, 2020, or 2021, but became more frequent in winter 2022 and 2023, Para-Influenza virus type 4 showed increased circulation beginning in autumn/winter 2022. In contrast, Para-Influenza virus type 2 exhibited minimal circulation throughout the study period (Figure 5). Figure 6 summarizes the overall circulation of respiratory viruses by season between 2019 and 2023.

Of the 564 positive PCRs, 450 were mono-infections (80%) and 114 were co-infections (20%). Of these co-infections, 108 were co-infections with 2 viruses and 6 co-infections with 3 viruses. Enterovirus/Rhinovirus was the most frequently implicated in co-infections, followed by Influenza A virus, RSV and Adenovirus. The most frequent association was Enterovirus/Rhinovirus + Influenza A found in 28 patients, followed by Enterovirus/Rhinovirus + Adenovirus in 19 patients, then Enterovirus/Rhinovirus + RSV in 13 patients and Enterovirus/Rhinovirus + Para-Influenza3 in 13 patients (Figure 7). No co-infections with Metapneumovirus or Coronavirus NL63 were detected.

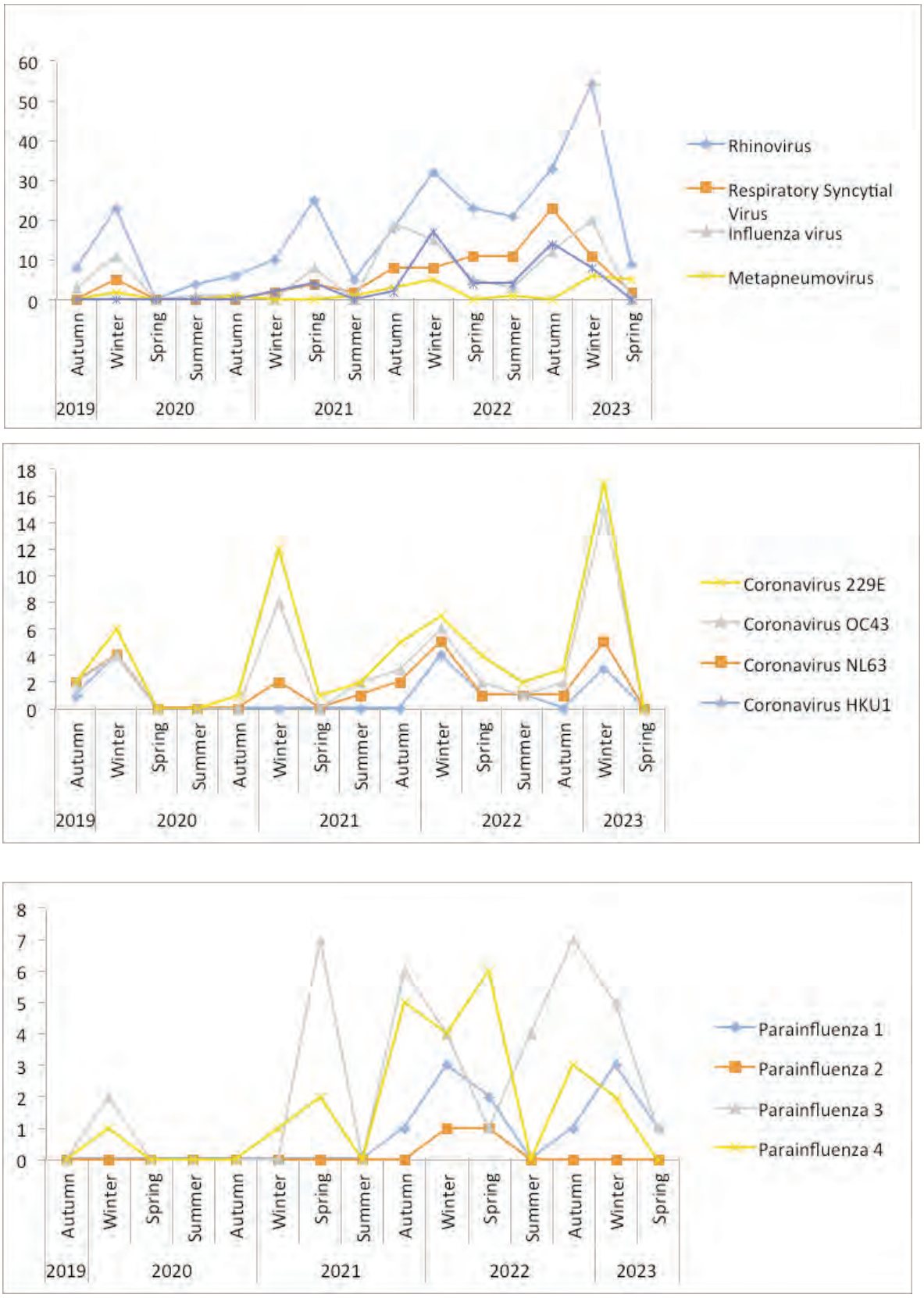

Figure 5 : Distribution of number of virus detected by seasons (N=564)

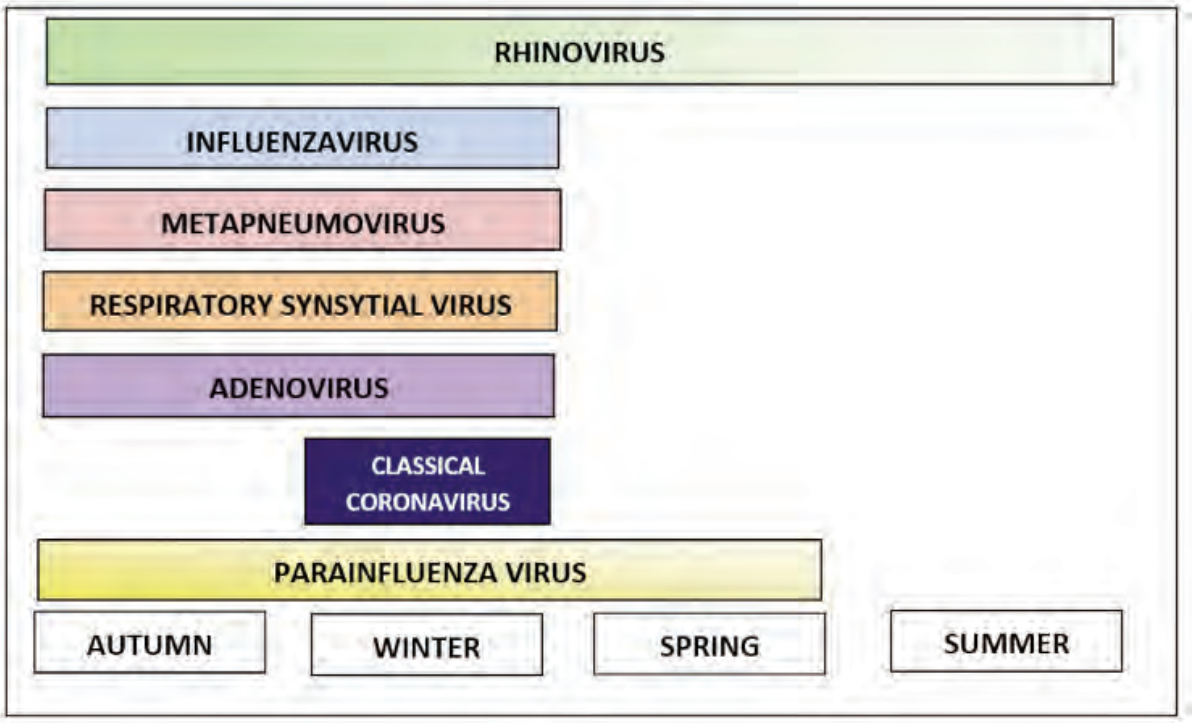

Figure 6 : Circulation of respiratory viruses by season between autumn 2019 and spring 2023

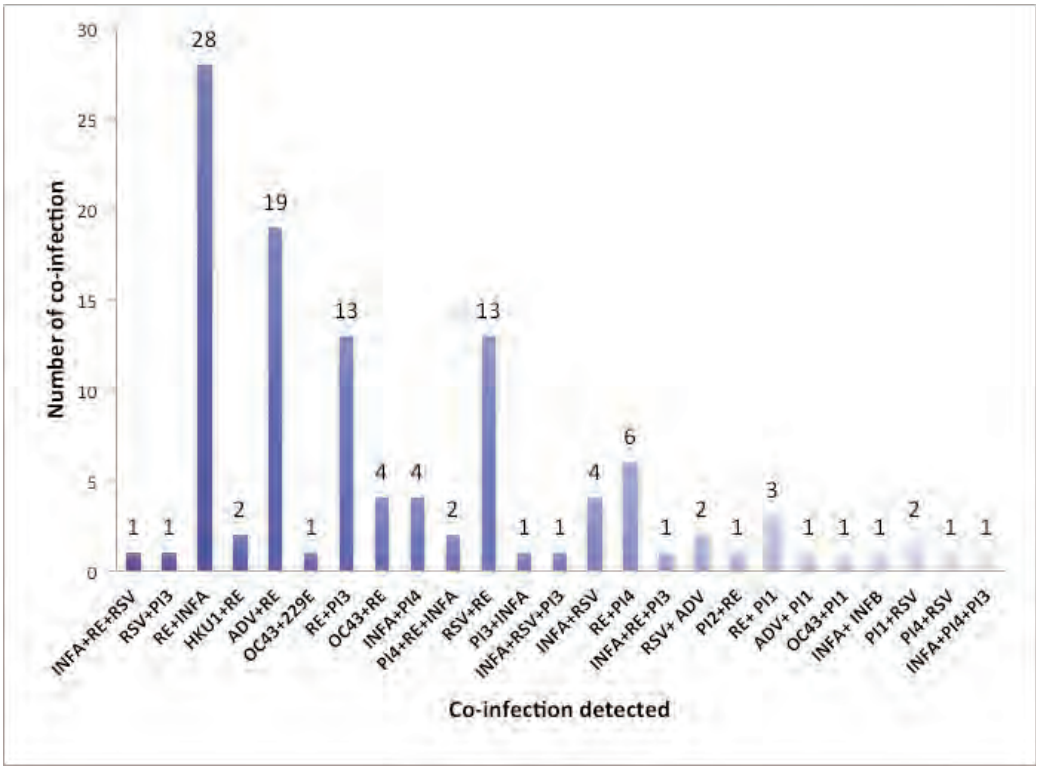

Figure 7 : Distribution of co-infections detected between autumn 2019 and spring 2023.

Abbreviations : INF: Influenza Virus, RE : Rhinovirus/Enterovirus, RSV : Respiratory Syncytial Virus, PI : Para-Influenza Virus, HKU1 and OC43 and 229E : Classical Coronavirus, ADV: Adenovirus.

DISCUSSION

The results of our study highlight a significant increase in the number of multiplex PCR requests over the years. This number increased from 103 in 2020 to 169 in 2021, then to 463 in 2022 and already reached 294 between January and April 2023. This upward trend is explained, on one hand, by the growing interest of clinicians in viral respiratory infections following the emergence of SARS-CoV-2 and on the other hand, by the prescribers' preference for an "all-in-one" diagnostic approach aimed at rapidly identifying the etiology and facilitating patient management. However, due to the high cost of these tests, rationalization of multiplex PCR prescribing is necessary (4). Relevant indications for multiplex PCR include: severe infections in elderly or immunocompromised patients with a negative monoplex test; pediatric cases with suspected severe or atypical pneumonia, bronchiolitis, or gastroenteritis; suspected atypical pneumonia (e.g. *Mycoplasma pneumoniae, Chlamydophila pneumoniae*) and investigation of community or nosocomial outbreaks with unknown etiology. In other contexts, a tiered diagnostic strategy using an algorithm combining monoplex and multiplex assays should be implemented. Studies conducted in Australia (5) and in Marrakech (6) reported contrasting findings, showing a decrease in the number of patients undergoing respiratory PCR testing after the onset of the COVID-19 pandemic. This reduction is likely attributable to a decline in hospital admissions and outpatient consultations.

In our study, the overall prevalence of respiratory viruses was 54% (564 patients). A study carried out at Marrakech University Hospital (6) reported a positivity rate of 59%, another study reported 48% in Rabat (1), while an Egyptian study (3) found a positivity rate of 59%. However, the study conducted in 2016 at the city of Shenzhen found a positivity rate of 14.55% (7). The positivity rate in our study was 57%, 53%, 72%, 52% and 44% in 2019 (September to December), 2020, 2021, 2022, 2023 (January to April) respectively. In 2020, the positivity rate was lowest due to the barrier measures and probably to reduced hospital recruitment. This was also the case in two studies carried out in Italy (8) and Korea (9), which reported respectively a positivity rate of 2% and 26% in 2020. The lifting of barrier measures in Morocco from June 2021 has been accompanied by a resumption of respiratory viruses with more severe clinical forms, due to a decline in population immunity associated with confinement.

Among the viruses detected in our study, Enterovirus/Rhinovirus mono-infections was the most frequently identified. Influenza was the second most frequent virus followed by RSV. The predominance of Enterovirus/Rhinovirus mono-infection has also been reported in several studies in the literature, independently of patient age and sex, notably the Italian study which found Enterovirus/Rhinovirus in 41% of cases (8).

In our study, the pediatric department had the highest positivity rate among the various departments, with a total of 168 positive cases (29%) followed by the clinical hematology department, Infectious Diseases Department and the pediatric intensive care unit. This result is in line with most studies in the literature, which report a higher prevalence of viral respiratory infections in the pediatric population. Indeed, the presence of respiratory symptoms in infants and newborns is often considered more alarming, and may lead to more frequent medical consultation than in older children or adults (10). Numerous studies have shown that infants represent the most affected age group, probably due to the immaturity of the immune system in infants and the absence of a history of exposure to respiratory viruses, which could increase their susceptibility (6,11). Enterovirus/Rhinovirus was predominant in all age groups studied, whether in adults (49%), children aged 0-5 (49%) or children aged 5-15 (50%); followed by Influenza virus, which was found mainly in adults (13%), while RSV, and Adenovirus were detected mainly in infants and children under 5 years.

In our study, male patients accounted for the majority in 60% of cases, with a M/F sex ratio of 1.52. The same trend was found in numerous studies carried out in Italy (1), Malaysia (12) and China (7) with M/F sex ratios of 1.54, 1.5 and 1.8 respectively. However, male predominance is not systematic and may vary from one study to another. A study carried out in Cambodia (13) showed a female predominance with a M/F sex ratio of 0.8. Male predominance could be explained by immune differences, due to a possible role for female hormones in the maturation of the immune system (14).

The circulation of respiratory viruses in our study was high during winter 2020. With the introduction of barrier measures in Morocco on March 2020, such as the wearing of masks, social distancing and confinement, the prevalence of respiratory viruses fell sharply. This decline has also been observed in other countries such as Taiwan (15), South Korea (16), United States, United Kingdom, Hong Kong and Singapore (17). With the gradual lifting of barrier measures in spring 2021, a rebound in respiratory viral infections has been observed with co-circulation of several viruses and a shift of the epidemic peak towards spring 2021.

The overall incidence of viruses was highest during the winter season (248 viruses detected), followed by autumn (155 viruses). This trend is confirmed by numerous studies conducted prior to SARS-CoV-2 in Canada, France and China which find annual seasonal outbreaks of respiratory viruses during the winter months (6). This can be explained by climatic factors such as ambient temperature and low relative humidity which favor virus survival in the environment and changes in host behav-

ior during the winter season, when individuals tend to spend more time indoors in enclosed spaces (6; 18). Prior to the COVID-19 pandemic, the seasonality of respiratory viruses was generally known. RSV, Influenza, Metapneumovirus and Coronaviruses mainly occurred in winter. Enterovirus/Rhinovirus, Para-Influenza and adenovirus infections are not markedly seasonal. Enterovirus/Rhinovirus causes an epidemic peak in autumn and spring (2). According to our study, after the lifting of the barrier measures, the overall circulation of respiratory viruses has been respected, excluding 2021 (peak shifted to spring) and the circulation of RSV during the summer of 2022. This is probably due to the absence of circulation of this virus and to the immune debt resulting from the lockdown.

In our study, the rate of co-infections was 20%, a rate comparable to that reported by Marrakech University Hospital study (20%) (6) and in a Chinese study (25%) (19). In Rabat, codetection was in 24% of positive samples (1). Two studies conducted in industrialized countries shown low rates (12% and 15% of cases) (20).According to an European study, the presence of co-infections correlates with more severe clinical signs, although this relationship is still widely debated (21). Furthermore, these codetections may correspond to co-infection, sequential infection, contamination, or cross-reaction. Hence, the fact that in the absence of quantitative results, these results remain insufficient, hence the interest of the threshold cycle (Ct) which provides a semi quantitative estimate of the viral load (1). The predominance of Enterovirus/Rhinovirus in cases of co-infections has been observed in several studies (22), which concurs with our results (93 cases). Among these cases, the most frequent association found in our study was Enterovirus/Rhinovirus + Influenza A (28 patients). In contrast, the most commonly reported association in one study was Enterovirus/Rhinovirus + RSV (21). The rate of co-infections increased significantly during the COVID-19 pandemic in our study, rising from 7% to 28% during the pandemic. This result is comparable to those of the study carried out in Marrakech (6). This increase can be explained by the fact that confinement measures and travel restrictions encouraged people to spend more time indoors, which may have favored the transmission of respiratory viruses, thus increasing the probability of co-infections.

Our study has certain limitations. Firstly, epidemiological and clinical data are limited due to the difficulty of accessing patient data in particular during the first year of the pandemic. Secondly, this is a monocentric study. Nonetheless, these results are a valuable aid in better orienting the actions of public services against viral respiratory infections and can serve as a basis for the development of a diagnostic algorithm according to the seasons and age of patients.

CONCLUSION AND RECOMMENDATIONS

Acute respiratory infections are common and frequent reason of medical consultations, particularly in children. They are associated with considerable morbidity and mortality. Molecular diagnosis of respiratory infections is indicated in specific situations. Multiplex PCR optimizes patient management and facilitates epidemiological surveillance of respiratory viruses. This epidemiological study shows the impact of the COVID-19 pandemic and the preventive measures introduced on the incidence of these viruses. Indeed, we have shown that the viruses most incriminated in our context are Enterovirus/Rhinovirus, Influenza virus and RSV.

In our context and according to the data from our study, it would be wise to prioritize the search for viral agents when faced with a respiratory picture. SARS-CoV-2 should be sought during peak epidemics, Enterovirus/Rhinovirus and Influenza virus can be tested first in adults, Enterovirus/Rhinovirus and RSV in children and infants. If the result is negative, in the case of a severe infection or a patient with risk factors, multiplex PCR can be performed. In autumn and winter, this test can be used to detect Metapneumovirus, Para-Influenza virus, Adenovirus and classical Coronavirus. In spring, Para-Influenza viruses can be targeted first. In summer, Enterovirus/Rhinovirus can be targeted first. Raising clinicians' awareness of the indications for multiplex tests would help optimize costs.

Data from the surveillance network and ongoing research in this field will contribute to a better understanding of the interactions between different respiratory pathogens, to improving the management and prevention of these infections, and to the early detection of a new emerging virological event (new virus, variant, nosocomial epidemic, etc.).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request. The data are not publicly available due to case-patient data reported in this analysis and is considered private information; we are unable to post to an open public repository.

ACKNOWLEDGEMENTS

The two first authors contributed equally to this work. The authors would like to thank all the healthcare of Mohammed V Military Teaching Hospital in Rabat, Morocco, who participated to this work.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

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