


Viral etiology of lower respiratory tract infections in adults in the pre-COVID-19 pandemic era: A cross-sectional study in a single center experience from Cameroon

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Abstract

Background and Aims: Respiratory viruses are responsible for the majority of lower respiratory tract infections (LRTIs) worldwide. However, there is a gap on the epidemiology of viral LRTIs in adults in sub-Saharan African countries. In Cameroon, like in other countries, the role of viral respiratory pathogens in the etiology of LRTIs in adults is helpful for clinical management. This study aimed to determine the viral aetiologies of LRTIs among hospitalized adults in a reference center for respiratory diseases in the town of Yaounde in Cameroon and its surroundings.

Methods: A cross-sectional study was conducted from January 2017 to January 2018 at Jamot Hospital in Yaounde (Cameroon). Clinical and demographic information; BAL and sputa were collected from hospitalized patients meeting LRTI case definitions. The clinical samples were investigated for respiratory pathogens with a commercial Reverse Transcriptase Real-Time Polymerase Chain Reaction (RT-PCR) targeting 21 viruses, cultures for bacterial and fungal infections.

Results: The 77 included adult patients with LRTIs had an appropriate clinical sample for microbial investigations. A viral agent was detected in 22.1% (17/77) samples. The main viruses detected included rhinovirus (10/77), coronavirus (hCoV-OC43 and hCoV-229E), and influenza A virus (3/77 each). A concomitant viral and bacterial co-infection occurred in 7.8% of patients (6/77) while viral co-infection occurred in one patient (1.3%). No Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in clinical samples. Most patients were under antimicrobials before getting diagnosed.

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Conclusions: Respiratory viruses account for 22.1% of LRTIs in hospitalized patients in this study. Despite prior antimicrobial therapy and delay, rhinovirus, coronavirus and influenza A virus were the most detected in patients in the pre-COVID-19 pandemic era in a single center experience from Cameroon.

KEYWORDS

adults, antimicrobials, lower respiratory tract infections, viruses

1 | INTRODUCTION

Lower respiratory tract infections (LRTIs) are a variety of illnesses made up of bronchitis, bronchiolitis, and pneumonia, and the major causes of morbidity and mortality out of infectious diseases globally.^{1,2} Annually, LRTIs cause approximately four million deaths³ and are the fourth cause of death worldwide.⁴ The percentage of disability-adjusted life years due to LRTIs in 2019 was estimated at 3.8.⁴ Large proportion of LRTIs are caused by viruses.^{5,6} The most commonly identified viruses are influenza, rhinovirus, respiratory syncytial virus, and coronavirus.⁷ Antibiotics are generally prescribed to patients with respiratory tract infections on a probabilistic basis in most health facilities in sub-Saharan Africa, and this can lead to antibiotic resistance.^{8–11} Many health systems in sub-Saharan Africa do not have an effective antimicrobial stewardship program because of the lack of a proper diagnostic technical platform.^{12,13} Selective use of antimicrobials based on proper diagnosis (i.e. evidence of differentiation of bacterial from viral infections) may strengthen antimicrobial stewardship.¹⁴ The lack of molecular platforms to differentiate respiratory viruses is a challenge for the clinical management of patients in resource-limited countries. Nucleic acid amplification tests (NAATs) have taken over as they have become a sensitive tool for diagnosing infections.¹⁵ Their use is restricted because of their exorbitant costs in the context of low-income countries.¹⁶ This can be explained by the few studies conducted to date exclusively on viral etiology of LRTIs in sub-Saharan Africa using NAATs.¹⁷ In view of the high cost of molecular analyses, it is through foreign aids that some NAAT platforms are set up through surveillance systems in low-income countries to improve diagnosis.

In Africa, there are limited data on the epidemiology of viral etiology of respiratory tract infections in adults. The available studies report the prevalence of viral etiology of respiratory tract infections that vary between 10% and 60%. In Egypt (North Africa), one study was done during the 2009–2010 pandemic on patients with pneumonia who tested positive for H1N1 (46.5%).¹⁸ Another study in the same ward reported 22.7% of viral respiratory infections among patients with LTRIs.¹⁹ In sub-Saharan African countries, studies done on respiratory tract infections reported a prevalence of 10.5% in Malawi²⁰ and 56.9% in Senegal²¹ among adult patients with influenza-like illness. A study in South Africa among adult patients with severe acute respiratory illness reported only a prevalence of 4% for respiratory syncytial virus without data on other targeted respiratory viruses.²² When focusing on studies of LRTIs in adults in sub-Saharan Africa, a large gap remains to be filled.

The studies in Senegal, Malawi, and South Africa relate to adult patients suffering from respiratory tract infections in general, without specificity on LRTIs. Studies in Cameroon on viral etiology of respiratory tract infections report data in children meanwhile, viral etiology in adults is difficult to estimate and poorly recorded.²³ This may be due to the fact that most studies in Cameroon selectively enrolled more children than adults through surveillance.²⁴ We undertook this study in a reference center for the management of respiratory diseases to determine the viral aetiologies of LRTIs among hospitalized adults to help avoiding unnecessary antibiotherapy.

2 | METHODOLOGY

2.1 | Study design

This cross-sectional study was carried out from January 2017 to January 2018 at Jamot Hospital in Yaounde, Cameroon. The Department of Pneumology of this hospital provides specialized services to patients with respiratory diseases in the political capital Yaounde and its surroundings. Participants were patients who met the LRTI case definition (bronchitis, bronchiolitis, and pneumonia)²⁵ and who gave their consent. A standardized questionnaire was used to collect data on the demographical and clinical parameters of participants. Participants diagnosed with only bacteria and tuberculosis were excluded in our analyses.

2.2 | Ethics approval

The study protocol was reviewed and approved by the National Ethics Committee for Research in Health before the start of the study (N°2017/03/876/CE/CNERSH/SP). All the participants and/or parents/legal guardians of those under 21 (age of majority in Cameroon) gave their written informed consent before enrollment.

2.3 | Sample collection

Sputa from the participants with productive cough and Bronchoalveolar-lavage (BAL) samples were collected as soon as possible after presentation at the hospital. Clinical samples were transported

at room temperature to Centre Pasteur du Cameroun (CPC) immediately after collection for diagnostic purposes. At CPC, samples were split into aliquots for bacteriology, mycology and virology. Samples for virology (1 mL) were put in a viral transport medium and kept at -80°C until RNA extraction.

2.4 | Virological investigations

The QIAamp Viral RNA Mini kit (Qiagen) was used to extract nucleic acid following the manufacturers' instructions with an internal control. An elution volume of 60 μL of RNA were obtained per extraction round and was stored in 1.5 mL Eppendorf tubes at -20°C till amplification within a week after extraction.

Amplification was done on the ABI prism 7500 using the Fast-Track Diagnosis Respiratory pathogens 33 (FTD-33), which is a commercial Reverse Transcriptase Real-Time Polymerase Chain Reaction technique. Extracted RNA (10 μL) was added to 15 μL of master mix (buffer, primers, probes, and enzyme). This amplification kit detects simultaneously 21 respiratory viruses: influenza A virus (FluA), influenza B virus, influenza A (H1N1) swl virus, influenza C virus, human rhinovirus (RV), human coronavirus NL63, human coronavirus hCoV-229E, human coronavirus OC43 (hCoV-OC43), human coronavirus HKU1, human parainfluenza 2, human parainfluenza 3, human parainfluenza 4, human parainfluenza 1, human metapneumoviruses A/B (HMPVA/B), human bocavirus, human respiratory syncytial viruses A/B (HRVA/B), human adenovirus, Enterovirus, and human parechovirus. The assay was validated when there was an amplification of the positive and internal controls and no amplification of the negative control.

To reassure of the non-circulation of Coronavirus Disease 2019 (COVID-19) during this pre-pandemic period, we re-analyzed the samples of these patients on the same real-time PCR platform for the search for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA sequence according to the Daan Gene Co., Ltd kit: Detection Kit for 2019 Novel Coronavirus (2019-nCoV) RNA (PCR-Fluorescence Probing). RNA was prepared fresh from samples stored at -80°C before SARS-CoV-2 testing.

2.5 | Statistical analysis

Data analyses were performed using the Statistical Package for Social Sciences software (version 22.0, SPSS Inc.). Chi-square test was used in the comparison of categorical variables. A p -value < 0.05 was considered significant based on one- or two-sided tests.

3 | RESULTS

3.1 | Participant characteristics and clinical diagnosis

Between January 2017 and January 2018, 108 participants with clinical evidence of LRTIs were enrolled in this study. Of them, 25%

(27/108) were suffering for tuberculosis (12 BAL and 15 sputa) and were excluded in our analyses. Four other participants were excluded because they were diagnosed only with bacteria in BAL (1 *Pseudomonas aeruginosa* and 1 *Citrobacter koseri*; 2 *Klebsiella pneumoniae*, and 1 *Enterobacter agglomerans*). The 77 participants considered in the analyses consisted of a male/female sex ratio of 1.1; with a median age of 54 years (range: 18.9–94 years). The preponderant symptoms observed were cough (80.5%), dyspnea (79.2%), asthenia (66.2%), fever (53.2%), and chest pain (45.5%). Sixteen point nine percent (13/77) of participants were under antipyretics and 72.7% under antimicrobials before their enrollment. Regarding the time of diagnosis, 67.5% (52/77) of the participants made an estimate on the date of onset of symptoms. Of these, 25% (13/52) presented to the hospital within 2 weeks of the date of first symptoms; and the others (39/52) came over 2 weeks. For HIV, 19.5% (15/77) of patients did not know their status. Other characteristics of the study participants are reported in Table 1.

3.2 | Viral and bacterial detections

Out of the 77 samples analyzed (42 sputa and 35 BAL), 22.1% [CI 95% (13.4%–33%)] were positive for one or more pathogens by FTD33. Six viruses were detected and the main one was RV at 13% (10/77). Other viruses included: 3.9% of FluA (3/77), 2.6% of hCoV-OC43 (2/77), 1.3% of hCoV-229E (1/77), 1.3% of HRVA/B (1/77), and 1.3% of HMPVA/B (1/77). Figure 1 indicates viral detection only in 2017, and Table 2 shows the different detection frequencies according to pathogens and type of clinical samples. RV pick was observed in March 2017 while two coronaviruses were detected in April 2017. The viral detection rate was 20% in BAL (7/35) and 23.8% in sputa (10/42). There was no association between clinical symptoms and detection of respiratory viruses ($p > 0.05$).

No SARS-CoV-2 was detected in patient samples in pre-COVID-19 pandemic in Cameroon.

3.3 | Co-infections

Table 2 shows co-infection levels following clinical samples. Mixed viral pathogens were reported only in one participant 1.3% (1/77). Viral and bacterial co-infections were reported in 7.8% (6/77) of participants. *H. influenzae* was co-detected in 29.4% of patients with viral infection (5/17).

4 | DISCUSSION

The viral causes of LTRI have received attention in recent years for the treatment of patients and compliance with antimicrobial stewardship. Here we give an overview on the viral etiology of LRTIs in the reference center for the management of respiratory

TABLE 1 Socio-demographic and clinical parameters of the study population.

Study population	Total (n = 77)	Positive viral samples (n = 17)
Median age in years (IQR)	54 (33.4–57.2)	38 (32.8–45.8)
18–35 years (young adults)	24	7 (41.2)
36–55 years (middle-aged adults)	31	8 (47.1)
>55 years (old adults)	22	2 (11.8)
Gender		
Female	37 (48.1)	7 (41.2)
Male	40 (51.9)	10 (58.8)
Under antimicrobials	56 (72.7)	13 (76.5)
Smoking habit	11 (14.3)	7 (41.2)
Overcrowding room	12 (15.6)	0
Median duration of symptoms in days before admission at hospital (IQR)	52.5 (15.8–120)	52.5 (8.8–90)
HIV	22 (28.6)	5 (29.4)
Clinical specimen		
Sputum	42	10 (58.8)
Broncho-alveolar-lavage	35	7 (41.2)
Clinical signs		
Cough	62 (80.5)	15 (88.2)
Dyspnea	61 (79.2)	14 (82.4)
Asthenia	51 (66.2)	13 (76.5)
Fever	41 (53.2)	9 (52.9)
Chest pain	35 (45.5)	10 (58.8)
Myalgia	19 (24.7)	5 (29.4)
Arthralgia	12 (15.6)	2 (11.8)
Sore throat	12 (15.6)	3 (17.6)
Headaches	11 (14.3)	3 (17.6)
Vomiting	9 (11.7)	3 (17.6)
Diarrhea	7 (9.1)	1 (5.9)
Rhinorrhea	6 (7.8)	1 (5.9)

Note: Percentage are in brackets; IQR, interquartile range; n, number.

diseases in the political capital of Cameroon in pre-COVID-19 pandemic era (with no SARS-CoV-2 detection).

Pathological samples from 77 patients suffering from LRTIs were subjected to viral investigations. With the molecular assay, viruses were detected in 22.1% of samples. Considering LRTI definition, our prevalence is low in comparison to 38–63% reported in Europe.^{26,27} The difference here could be due to many reasons. Patient diagnosis delay before the first clinical symptoms and socioeconomic challenges could be some predictable factors. Different sampling

techniques, detection methodologies, case definition of respiratory infection, and geographical areas can greatly influence the observed burden from each virus.¹⁶ Indeed, it has been shown that the greater the number of days between symptom onset and sample collection, the more difficult it is to detect a causative viral agent.¹⁶ In the present study, median time before admission at the hospital was 52.5 days. Most respiratory viruses are present in high titers in the respiratory tract in the first 3 days after symptom onset.¹⁶ In the context of low-income countries, delays are common issues since most patients are not able to afford the costs of medical care.^{28,29} This sometimes make their health situation worse by the time they come to the hospital, especially when they have already started self-medication which is strongly discouraged.³⁰ As in clinical trials, this kind of study is a way to get diagnosed free of charge.³¹ As such, by the time of viral investigations, patients could have already eliminated the viruses even if molecular tool remains a sensitive method for virus detection even after 2 weeks after symptom onset.¹⁶ Viral infections occur mostly in acute phases of diseases, less than 15 days.³² Our findings are comparable to detection rates of 21%–33% reported in some studies on inpatients with LRTIs in sub-Saharan African countries such as Malawi^{33,34} and Kenya.³⁵ The same trends are reported in PCR-based studies, which show evidence of viral infection among adults with LRTIs.^{36,37} Taking in account the case definition of LRTIs, a similar prevalence (22.7%) has been reported in adult patients in northern Africa (Egypt) earlier.¹⁹ But we should be aware that the current molecular assay targets more pathogens (21 viruses) than those reported in previous studies³³ and could impact the viral detection rate.

The detection of viruses was similar in sputa and BAL (between 20% and 24%). RV was the most common pathogen detected (13%) followed by human coronaviruses (3.9%) and Influenza A virus (3.9%). These detection rates were slightly low compared to 20.1% and 7.4%, respectively for RV and coronaviruses among adults with LRTIs in primary care networks in Europe.²⁶ Variations in detection rates may be related to differences in study populations, locations, study periods, environmental factors, the number of viral pathogens tested, and differences in diagnostic techniques.³⁸ Our findings highlight RV as one of the most detected viruses in hospitalized adult patients like in Europe²⁶ and also in Sub-Saharan Africa (Kenya and Malawi).^{33,35}

Co-infection rate was 9.1%, viral-bacterial mixed infection accounted for 7.8%, and mixed viral infection of HMPVA/B and RV rate was 1.3% for all samples. *H. influenzae* was co-detected in one-third of infected participants with respiratory viruses. Compared to other studies in Africa, co-infection rate was low, and pneumococcus is the bacterium more involved in respiratory infections more than *H. influenzae*.^{33,35} RV has been reported among the leading viral pathogens involved in mixed viral infectious agents.³⁹ Viral co-infection or the detection of two or more pathogens in a single patient may be attributed to asymptomatic persistence or the shedding of viruses.⁴⁰ Indeed, molecular assay is the most useful method to detect co-infections representing near-past and current infections, because of its ability to detect very low viral titers and/or lingering nucleic acid still present later in the infection course.¹⁶

Trends of virus detection (in 2017)

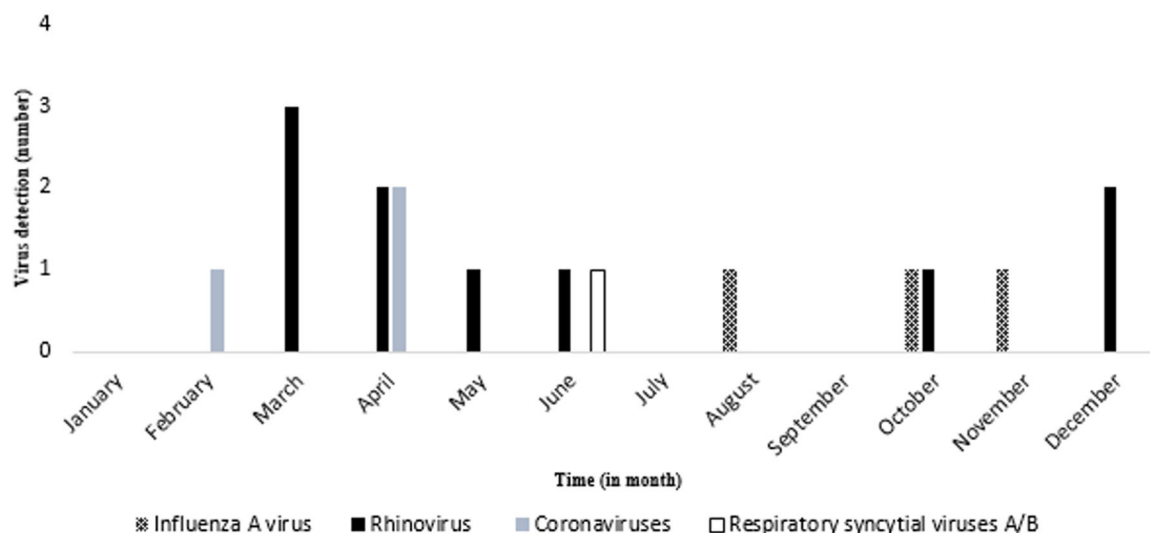


FIGURE 1 Trends of virus detection in LRTI patients over time. More viruses were detected during the second and fourth quarters of the year 2017.

TABLE 2 Level of co-infection in lower respiratory tract by FTD-33.

Infection level	Pathogens	Number	Clinical samples
Single viral infection	HRSVA/B	1	BAL
	RV	6	1 BAL + 5 Sputa
	hCoV-OC43	1	Sputum
	FluA (1 H1N1)	2	BAL
Viral\co-infection	RV + HMPVA/B	1	BAL
Viral and bacterial co-infection	FluA (H1N1) + <i>Haemophilus influenzae</i>	1	Sputum
	RV + <i>Klebsiella pneumoniae</i>	1	BAL
	hCoV-229E + <i>Haemophilus influenzae</i>	1	Sputum
	hCoV-OC43 + <i>Haemophilus influenzae</i>	1	BAL
	RV + <i>Haemophilus influenzae</i>	2	Sputum

Abbreviations: BAL, bronchoalveolar lavage; FTD-33, Fast-Track Diagnosis Respiratory pathogens 33; FluA, influenza A virus; H1N1, influenza A (H1N1) swl; hCoV-229E, coronavirus 229E; hCoV-OC43, coronavirus OC43; HRSVA/B, human respiratory syncytial viruses A/B; HMPVA/B, human metapneumo papilloma virus A/B; RV, rhinovirus.

The limitations of this study are delay, and prior antimicrobial therapy of patients that could be biased for real pathogen frequencies reported. Prior antimicrobial therapy of patients was 72.7% which is high compared to studies in developing countries with is around 39%⁴¹ and constitutes a major issue for viral

investigations. In Africa, self-medication with antibiotics, for example, ranged from 12.1% to 93.9% with a median prevalence of 55.7%.⁴² Pooled prevalence of self-medication with antibiotics is 78% in low-and-middle-income countries⁴³ for which the data from the present study are in accordance. Self-medication in Africa is well known, and the lack of national programs for the proper use of antimicrobials added to street drugs represent a real threat to the future of the continent. Resistance to antimicrobials is going to be a major cause of death in the next decades since some estimates show that by 2050, antimicrobial resistance could cause 10 million deaths annually.⁴⁴ Data in 2019 revealed that antimicrobial resistance was associated to 4.95 million deaths, an estimate which is higher than the combined number of people who died from HIV/AIDS and malaria the same year.⁴⁵ The studies carried out in Africa on the viral etiology of LRTI to date on the prior use of antimicrobials do not focus on this phenomenon, and our findings ring the alarm bell on the risk linked to self-medication and access to street drugs.

This work, being of a pilot nature, raises implications for surveillance and future research. The present study shows a high prevalence of viruses in adults with LRTIs in Cameroon. It is therefore important to continue the detection of respiratory viruses continuously to determine their seasonality in subjects with LRTIs to plan the appropriate timing of the administration of vaccines for viruses such as Influenza. Improving surveillance systems to include more adults would be a key step in reducing unnecessary antibiotic prescriptions (to prevent the development of antimicrobial resistance) and in managing and preventing LRTIs in general. This could be done by the selection and continuous monitoring of the majority viruses in the LRTIs in our resource-limited setting. Further studies will also help us to determine the etiological roles of these respiratory viruses in the clinical presentation of LRTI in adults.

5 | CONCLUSION

Results from one year study on viral aetiologies of LRTIs in hospitalized adult patients before the COVID-19 era provided important insight. Viral etiology was established in 22.1% of cases. RV, coronaviruses, and FluA were the most detected viruses. Many patients come to hospital with delay after failure of self-medication which is crucial when managing LRTIs. The data show that in the pre-COVID-19 pandemic era in a single centre experience from Cameroon, coronaviruses were detected in hospitalized adults with LRTIs.

AUTHOR CONTRIBUTIONS

Serges Tchatchouang: Data curation; formal analysis; investigation; methodology; validation; writing—original draft; writing—review & editing. **Sebastien Kenmoe:** Methodology; validation; writing—review & editing. **Ariane Nzouankeu:** Methodology; validation; writing—review & editing. **Mohamadou Njankouo-Ripa:** Methodology; validation; writing—review & editing. **Veronique Penlap:** Methodology; supervision; validation; writing—review & editing. **Valerie Donkeng:** Methodology; validation; writing—original draft. **Eric-Walter Pefura-Yone:** Investigation; methodology; validation; writing—review & editing. **Marie-Christine Fonkoua:** Investigation; methodology; project administration; supervision; writing—review & editing. **Sara Eyangoh:** Conceptualization; methodology; project administration; validation; writing—review & editing. **Richard Njouom:** Conceptualization; methodology; project administration; supervision; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest. Supporting source/financial relationships had no involvement in study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

DATA AVAILABILITY STATEMENT

Data are available at Centre Pasteur du Cameroun and can be accessed via proper request to the corresponding author.

ETHICS STATEMENT

The study protocol was reviewed and approved by the National Ethics Committee for Research in Health before the start of the study (N°2017/03/876/CE/CNERSH/SP).

PATIENT CONSENT STATEMENT

All the participants and/or parents/legal guardians of those under 21 (age of majority in Cameroon) gave their written informed consent before enrollment.

TRANSPARENCY STATEMENT

The lead author Richard Njouom affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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