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## CLINICAL PHARMACOLOGY

# Impact of the COVID-19 pandemic on antiviral drug development for other community-acquired respiratory viruses' infections

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**Summary** The coronavirus disease 2019 (COVID-19) pandemic indirectly resulted in missed therapeutic opportunities for many diseases. Here we focus on community-acquired respiratory viruses other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [respiratory syncytial virus, parainfluenza and influenza A], and highlight the pandemics impact on clinical trials to develop novel therapies for other severe respiratory viral infections. We retrospectively reviewed inclusion rates within respiratory antiviral clinical trials in comparison with all other clinical trials in our clinical investigations center, before and during the COVID-19 pandemic. As opposed to the remaining clinical trials developed within our unit, respiratory antiviral trials inclusion rates did not recover after the initial recruitment decrease observed across all trials during the first pandemic wave. These results were discussed in the context of non-COVID-19 respiratory viral infection rates within our center, showing a general decline in seasonal respiratory viruses spread since the COVID-19 pandemic onset. Virus epidemiology

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changes upon the wide SARS-CoV-2 expansion as well as the lifestyle changes globally adopted to prevent SARS-CoV-2 transmission could have therefore contributed to the negative impact of the COVID-19 pandemic on antiviral drug development. Our study highlights the peculiarity of respiratory antiviral drug development during the COVID-19 pandemic era and describes potential explanations for such drug development halting.

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## Abbreviations

|           |                                                 |
|-----------|-------------------------------------------------|
| CIC       | clinical investigation center                   |
| COVID-19  | coronavirus disease 2019                        |
| HSCT      | hematopoietic stem cell-transplanted patient    |
| PCR       | polymerase chain reaction                       |
| PIV       | para influenza virus                            |
| RSV       | respiratory syncytial virus                     |
| SARS-CoV2 | severe acute respiratory syndrome coronavirus 2 |

## Brief report

Seasonal respiratory viral infections such as respiratory syncytial virus (RSV), influenza A virus and para influenza virus (PIV) infections share many common features, including their respiratory transmission route and a similar host population at higher risk of developing a severe disease. Such viruses result in aggressive infections among immune-compromised patients and particularly hematopoietic stem cell-transplanted patients (HSCT) who can develop severe respiratory symptoms leading to increased hospitalization rates, intensive care requirement and immune-related complications such as lung chronic graft-versus-host-disease and death [1]. To date, there are few or no approved effective therapeutic options, and treatment of these patients mainly relies on symptomatic measures (oxygen therapy and mechanical ventilation). Targeting such infections is intrinsically challenging and remains an unmet clinical need to decrease their related morbidity and improve patients' survival [2].

Our clinical investigations center is dedicated to multi-disciplinary clinical trials and has pioneered a number of early drug development studies over the past decade. According to our hospital site specificities combining a large dedicated allogeneic HSCT unit and a respiratory diseases department specialized in hematological patients' complications, many respiratory antiviral clinical trials aiming at increasing therapeutic options for such patients have been performed within our unit since 2014. The desired profile for such new antivirals would be as follows: rapid onset of protective effects; better activity in patients with high viral load; inhibition of both virus production and release; maintenance of activity against viral receptors;

maintenance of potency against resistant viral strains; safety and good tolerability.

Unlike RSV, Influenza A and PIV, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus displayed a non-seasonal infection pattern in 2020. The characteristics of the SARS-CoV-2 pandemic, including its non-seasonality could strongly impact epidemiological dynamics of other viral respiratory infections [3]. Since its onset in March 2020, the COVID-19 pandemic has also changed our way to manage patients with increasing use of telemedicine; most immune-compromised patients being followed as outpatients to prevent SARS-CoV-2 contamination. Additionally, the pandemic heavily impacted our lifestyle; implementing SARS-CoV-2 transmission preventive measures such as physical and social distancing, hand washing, and the use of face masks. All together, these measures could hamper patient recruitment within respiratory antivirals clinical trials, therefore profoundly affecting drug development for RSV, Influenza A and PIV.

Here, we report a monocentric retrospective study, to evaluate the impact of the coronavirus disease 2019 (COVID-19) pandemic on non-SARS-CoV-2 respiratory antivirals clinical trials and discuss the challenges for such treatments early drug development in the COVID-19 era.

## Methods

Patient inclusion rates within respiratory antiviral clinical trials in our clinical investigations center (CIC-1427), before and during the COVID-19 pandemic were collected within our center between 2014 (time of first respiratory antiviral clinical trial initiation in our unit) and 2021. Non-COVID-19 respiratory viral infection rates (RSV, PIV and influenza A) identified by real-time polymerase chain reaction (PCR) within our center were also collected.

To identify factors responsible for the COVID-19's pandemic impact, recruitment specificities of respiratory antiviral clinical trials and the set of COVID-19 health measures implemented in our center are also described.

In addition, as a comparative element, global patient inclusion rates and the number of clinical trials initiated within our center across all diseases were also collected between 2014 and 2021. Among these trials, nine included non-viral respiratory diseases (eight lung cancer cohorts as

part of pan-cancer phase I/II clinical trials, one clinical trial for bronchiolitis obliterans syndrome).

At time of the COVID-19 pandemic onset, 129 clinical multidisciplinary trials were active in our center (Fig. 1A).

Between 2014 and 2021, five phase II and two phase III clinical trials aiming at assessing the efficacy and tolerability of novel antiviral therapies for patients at-risk of severe upper and/or lower respiratory tract viral infections, have been initiated within our center (Fig. 1B). Among these studies, three were phase II studies evaluating the antiviral effects, pharmacokinetics, safety and tolerability of new molecules in RSV-infected HSCT patients, one phase II study aimed to include patients with RSV infections requiring a hospitalization, two studies (phase II and phase III) focused on influenza A hospitalized patients, and one phase III study was dedicated to PIV infections in immune-compromised patients. Fifteen patients were included in the four trials that were completed prior to the COVID-19 pandemic, while none was included in the three trials open for recruitment during the pandemic period (Fig. 1B). All three studies open for recruitment during the COVID-19 pandemic period were ultimately stopped by sponsor decision due to lack of recruitment prospects. Additionally, no study was initiated in our site since the COVID-19 pandemic outbreak in March 2020, due to sponsors' decision given the limited to almost non-existent number of candidates for such clinical trials. No trial evaluating respiratory antivirals is currently recruiting within our center.

To evaluate whether such decrease in patients' recruitment and study initiations was due to healthcare authorities' recommendations issued during the pandemic [4,5], we compared inclusion rates and new study initiations for respiratory antiviral drug development with those of studies aiming at developing new drugs for all other diseases within our multidisciplinary clinical investigations center. Interestingly, while we observed a 37% decrease in patients' enrollment in 2020 in comparison to the pre-pandemic era (2019), recruitment rates increased immediately after, reaching the pre-pandemic level of recruitment in 2021 (Fig. 1C). Indeed, 25 new trials have been initiated in 2021 and 131 trials are currently active within our center (Fig. 1C). Among the newly initiated clinical trials, the majority aimed at enrolling patients with oncological diseases (11 onco-dermatology and 11 onco-hematology clinical trials). The remaining trials included a dermatomyositis, an aplastic anemia and a SARS-CoV-2 vaccine clinical trial.

Our data therefore highlight the peculiarity of antiviral treatment development. Such impact on respiratory antiviral clinical trials development, could rather be due to virus epidemiology changes upon the wide SARS-CoV-2 expansion and the lifestyle changes globally adopted to prevent SARS-CoV-2 transmission. Since SARS-CoV-2 is the predominant virus in this new respiratory virus epidemiology landscape, an unfavorable viral competition for the other respiratory viruses could explain patients' recruitment decrease. Indeed, according to our local seasonal virology surveillance data, a general decline in seasonal respiratory viruses (RSV, PIV and Influenza A) spread has been observed since the COVID-19 pandemic onset (Fig. 1D). Notably, such decrease in the number of infections was not related to a reduced number of real-time PCR testing. The mean ratios of positive to total number of PCR's performed in our center were 4.0%

(mean annual tests: 3350), 4.5% (mean annual tests: 2061) and 7.1% (mean annual tests: 3324) for RSV, PIV and Influenza A respectively during the pre-pandemic period (2014-2019), while being decreased to 1.7% (mean annual tests: 3335), 1.5% (mean annual tests: 2876) and 1.2% (mean annual tests: 3318) during the COVID-19 pandemic (2020-2021).

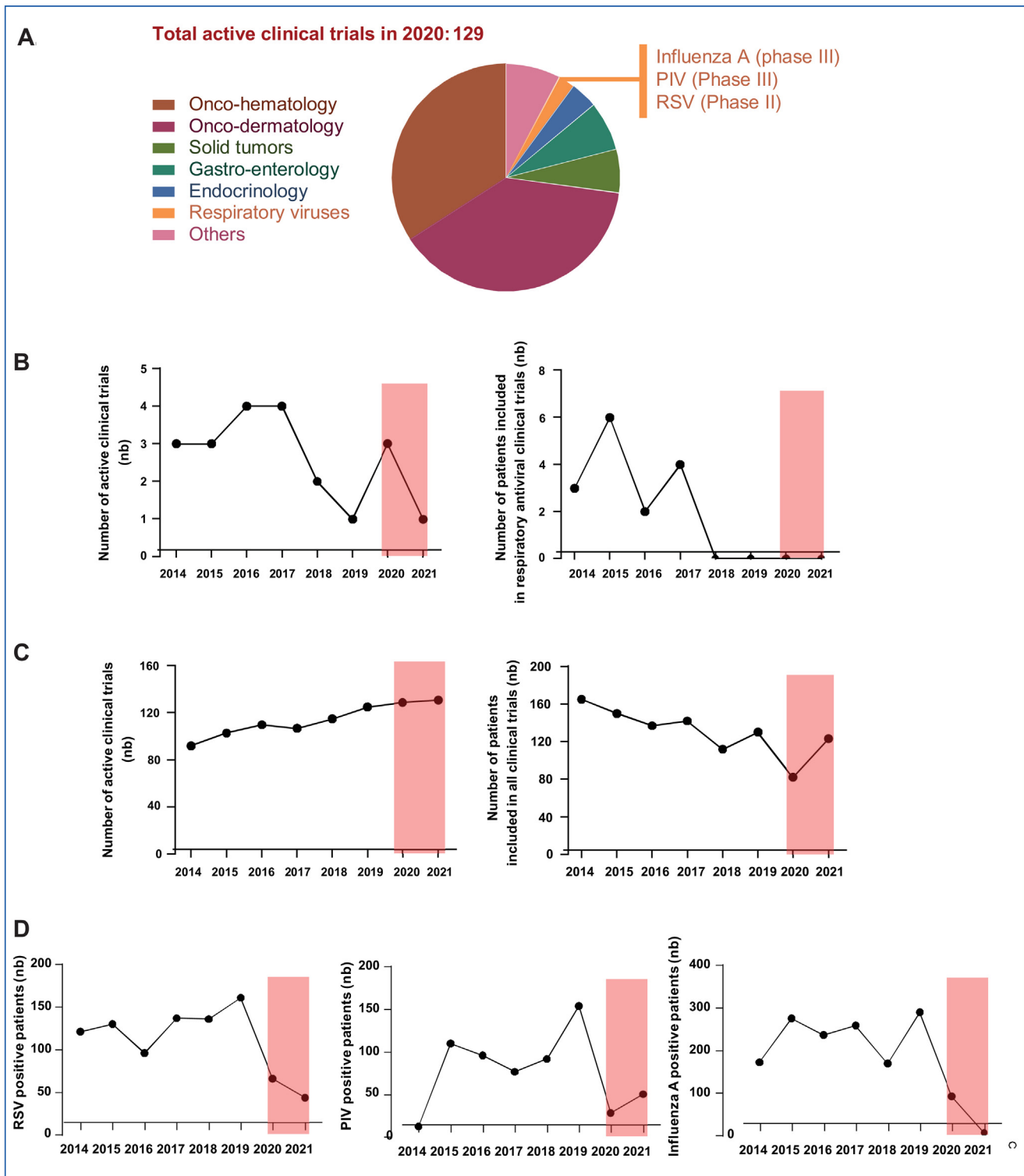
## Discussion

We recently reported on our efforts to pursue patients care within early phase clinical trials during the pandemics first-wave and the concomitant national lockdown [6]. Our internal reorganization (telemedicine, treatments shipment, remote-monitoring) allowed pursuing the needed care for patients included in clinical trials, many of which have limited therapeutic alternatives. However, according to health regulatory organizations, new clinical trials initiation has been significantly delayed [4,5]. One year later, clinical trials initiation globally increased within our center to reach the pre-pandemic level.

As reported in our study, respiratory antiviral clinical trials represent an exception as no new trial has been initiated and all ongoing trials have been definitely closed by sponsor's decision, prior to reaching the expected patient inclusion numbers. Clinical trials evaluating new antiviral therapies have therefore paid a heavy price.

The COVID-19 pandemic has been accompanied by a multi-factorial shift in respiratory viral epidemiology due to the high rate of SARS-CoV-2 infections on one hand, and the respiratory virus transmission preventive methods implemented within our lifestyle on the other hand. Indeed, influenza A, RSV and PIV viruses present systematically between fall and spring did not occur in both hemispheres during the COVID-19 pandemic period as reported by several studies [7–10]. Although the pattern in which respiratory viruses will coexist and their seasonality once the COVID-19 pandemic under control or when it will become seasonal remains to be seen, an increase in other respiratory viruses will likely be observed and requires a thoughtful management plan for immune-compromised patients. Importantly, Van Summeren et al. and Zheng et al. recently suggested that the RSV seasonal epidemiology could be modified in the post-COVID-19 era, highlighting the importance of a year-round RSV surveillance [11,12]. Despite having precluded drug development for other respiratory viruses, some positive aspects could result from the healthcare advancements developed to manage the COVID-19 pandemic. Developing rapid detection tests and generalizing the use of self-tests in high-risk populations, will help identifying patients at time of symptoms onset therefore overcoming one of the major pre-pandemic recruitment challenges to accelerate antiviral drug development. A key recruitment element is indeed the need for study patients' selection immediately after symptoms onset. Additionally, preventive measures such as physical and social distancing, quarantines and curfews, facial masks wearing and hands hygiene may also be highly effective on the spread of seasonal viruses. Finally, the pharmacological development of COVID-19 vaccines highlighted important social pharmacology perspectives [13].

Limitations of our study mainly lie on a low recruitment rate prior to the COVID-19 pandemic. Although being low,



**Figure 1.** A: Active clinical trials within our clinical investigations center at time of the COVID-19 pandemic onset, classified by disease type. B: Active clinical trials evaluating novel respiratory antiviral drugs within our clinical investigations center, between 2014 and 2021. The red box highlights the COVID-19 pandemic period. C: Active clinical trials within our clinical investigations center, between 2014 and 2021. The red box highlights the COVID-19 pandemic period. D: Respiratory syncytial virus (RSV), Para influenza virus (PIV), Influenza A and SARS-CoV-2 annual incidence within our center between 2014 and 2021. Molecular detection was performed on nasal swabs using quantitative PCR analysis. The red box highlights the COVID-19 pandemic period. COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction; SARS-CoV2: severe acute respiratory syndrome coronavirus 2.

our centers' inclusion rates were in the higher-range when compared to the total number of recruiting centers. Pre-pandemic low inclusion rates are inherent to such clinical trials due to:

- a rare target/eligible patients' population given the uncommon aggressiveness of such diseases among healthy individuals;
- a reduced recruitment period given the winter seasonality of respiratory virus infections;
- and a straight therapeutic time interval after infection given the need of treatment initiation quickly after symptoms onset, therefore requiring a rapid coordination between emergency and pneumology departments, virology units and clinical investigation centers.

In conclusion, our study highlights the peculiarity of respiratory antiviral drug development during the COVID-19 pandemic era, describes the potential explanations for such drug development halting, and suggests potential positive aspects to learn from this experience. Lack of preventive and curative therapeutic options for immune-compromised patients with respiratory viral infections raises the necessity of foreseeing the future of antiviral drug development in the post-COVID-19 era.

## Authorship contribution

C.D.S. and S.A. collected the data. M.S. and J.L.G. collected and analyzed virological data. D.M., J.J. K and A. B. were involved in patients care. Z. G., A.B. and L.B. designed the study, analyzed the data and wrote the manuscript. Z.G. supervised the study. All co-authors reviewed, edited and critically discussed the manuscript.

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## Disclosure of interest

L.B. has received research support from the GILEAD foundation for research projects unrelated to the current study. A.B. and D.M. were co-investigators of the described clinical trials. Z.G., M.S., S.A. and J.L.G. were involved in on-site clinical trials conduct. The remaining authors declare no competing interests.

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