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RECOMMENDATIONS FOR COVID-19 PREVENTION AND TESTING FOR HEMATOPOIETIC CELL TRANSPLANT CENTERS IN BRAZIL - SEPTEMBER 2023

Ana Verena de Almeida Mendes[1], Fabianne Carlesse[2], Jessica Ramos[3], Márcia Garnica Maiolin[o4] Clarisse M. Machado[5,6], SBTMO INFECTIONS GROUP

1 Hospital São Rafael, Universidade Baiana, Brazil
2 Universidade Federal de São Paulo - UNIFESP/EPM, Brazil
3 Hospital Sírio Libanês
4 Universidade Federal do Rio de Janeiro, Complexo Hospitalar de Niterói, Brazil
5 Laboratório de Virologia, Instituto de Medicina Tropical da faculdade de Medicina da USP, Brazil
6 Serviço de TMO, Hospital Amaral Carvalho, Jaú, Brazil

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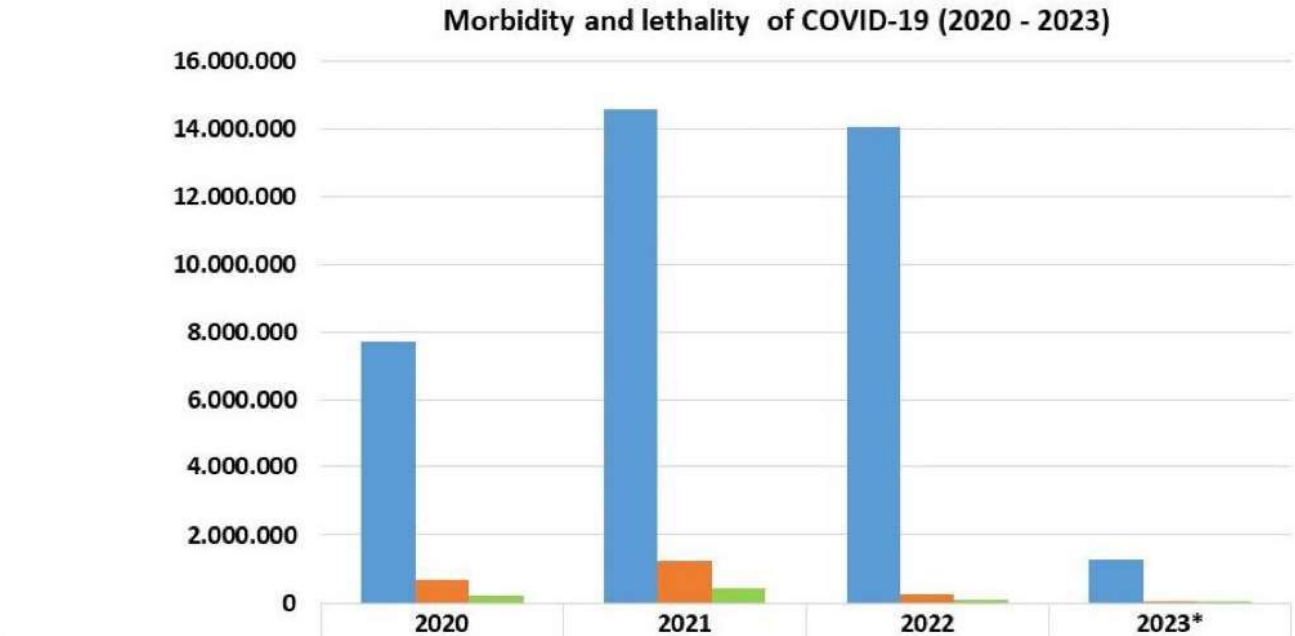
CURRENT SITUATION OF COVID-19

From February 2020 to May 2023, 37,625,916 cases of COVID-19 were recorded in Brazil, which led to 2,173,359 hospitalizations due to severe acute respiratory syndrome (SARS) with 703,291 deaths due to COVID-191. More than 14 million cases were registered in 2021 and 2022. However, there was a significant drop in the number of hospitalizations for SARS and the COVID-19 fatality rate in 2022, which certainly reflects the impact of mass vaccination in the country, started in February 2021 (figure 1).

FIGURE 1. Number of COVID-19 cases, SARS hospitalizations and COVID-19 deaths (2020-2023).

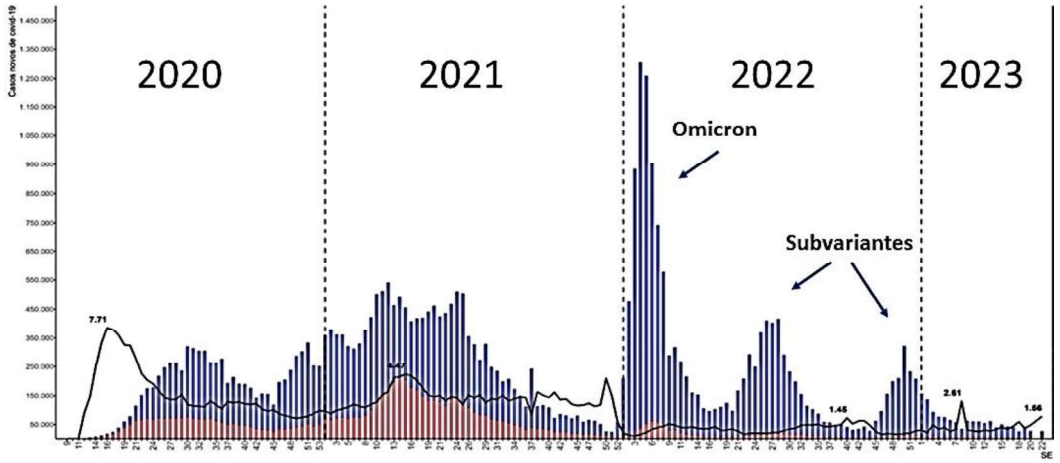


	2020	2021	2022	2023*
COVID-19 cases	7.716.405	14.575.102	14.039.774	1.294.635
SARS hospital admissions	700.565	1.214.520	235.568	22.706
COVID-19 deaths	195.725	423.380	74.748	9.438

The appearance of the Omicron variant of concern at the beginning of 2022 justifies the large number of COVID-19 cases in this period given its high transmissibility, but with lower hospitalization and death rates, due to the progressively greater number of vaccinated individuals.

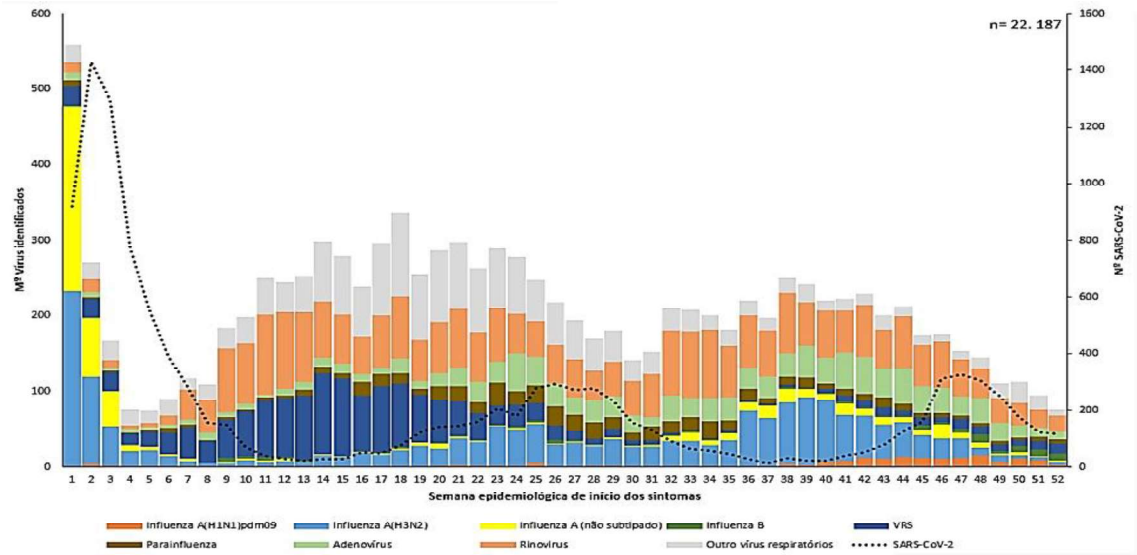
The great replication capacity of the Omicron variant has led to the rapid emergence of sub variants, leading to episodic increases in COVID-19 cases across the country (figure 2).

FIGURE 2. Cases, deaths and fatality rate from COVID-19 from 2020 to 2023[1]



It is very important to remember that the year 2022 also brought the return of other respiratory viruses (RV), which disappeared from the diagnosis scenario due to the high circulation activity of SARS CoV-2 and the containment measures implemented (use of masks, frequent hygiene of hands, use of alcohol gel, social distancing, etc.). With the reduction in the circulation of SARS CoV-2, other respiratory viruses began to circulate again. Figure 3 clearly shows the return of circulation of respiratory viruses throughout 2022[2].

FIGURE 3. Circulation of respiratory viruses in Brazil in 2022[3]



COVID-19 IN HCT RECIPIENTS PRE- AND POST-VACCINATION

Pre-vaccination data shows a high lethality of COVID-19 in allogeneic and autologous HCT recipients in Brazil and around the world (table 1).

TABEL 1. COVID-19 lethality in unvaccinated HCT recipients[4]

Author, year	N	Lethality	Risk factors for death
Sharma et al., 2020	318	32%	<50 years, masculine, 1º year CTH
Shah eet al., 2020	72	22%	-
Coll et al., 2020	85	20% alo; 24% auto	-
Varma et al., 2020	25	21%	Age, corticosteroid, 1º year CTH
Piñana et al., 2020	123	18% alo; 17% auto	Age, hypertension, PCR>20 mg/dL, lymphopenia
Ljungman et al., 2021	382	28,5% alo; 28% auto	Age, performance and ICU admission
Daudt et al., 2022*	86	15% alo; 36% auto	Age, performance and orotracheal intubation

In the pediatric population, SARS CoV-2 infection is often asymptomatic (30% to 40% of cases), and 47% of children have mild forms of COVID-19. However, approximately 10% of children can develop severe forms of the disease with fatality rates ranging from 3% to 8%[5,6].

Despite the intense circulation of the Omicron strain in 2022 and its subvariants, the morbidity and lethality of COVID-19 decreased with the progressive advancement of vaccination among HCT recipients as observed in the general population, demonstrating the capacity to respond to vaccination in this population.

A study carried out in a single Brazilian center including 174 cases of COVID-19 in HCT recipients showed a drop in COVID-19 lethality from 14.2% between May 2020 and May 2021, to 8% between June 2021 and May 2021. 2022. In this center, the lethality of COVID-19 was significantly higher in recipients of autologous HCT (23.5%) compared to allogeneic (4.7%)[7].

Meta-analyses of studies evaluating the humoral and cellular response to vaccination against COVID-19 showed a serological response in around 80% of recipients, slightly higher in autologous HCT compared to allogeneic[8,9]. Although the intensity of the antibody response was lower than that induced by COVID-19 vaccines in the general population, mass vaccination marked the easing of the pandemic and its impact on HCT centers.

It was three years of many sacrifices, hard work and a lot of sadness, but also of victories and achievements: better awareness of the importance of respiratory viruses and their transmission mechanisms, and greater adherence to control measures. Hand hygiene, use of masks, cough toilet, social distancing, etc., were measures incorporated into the daily routine not only of patients, but of the society as a whole. We gain access to systematic COVID-19 testing for candidates, recipients, donors, healthcare professionals, among others.

SYMPTOM SURVEILLANCE AND PRE-ADMISSION TESTING OF SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

It is important to remember that the recommendation for surveillance of respiratory symptoms and systematic testing of symptomatic candidates before admission for HCT precedes the COVID-19 pandemic[10]. This recommendation was initially justified by the high morbidity and mortality of respiratory syncytial virus (RSV) pneumonia in the first month of transplantation and the risk of transmission in the HCT unit. The opportunity to test asymptomatic patients can help the decision of postponing the transplantation in case of a positive test, since the risk of progression to RSV pneumonia is high if HCT is not postponed until symptoms resolution[11].

Subsequently, this recommendation was extended also to other respiratory viruses since they all present great morbidity, especially in the pre-grafting period[10,12,13]. Table 2 shows the incidence, frequency of pneumonia and mortality in hematological patients and HCT recipients, according to the respiratory virus diagnosed.

TABLE 2. Incidence, frequency of pneumonia and mortality from respiratory viruses[12]

Respiratory viruses	Incidence (%)	Pneumonia in diagnosis (%)	Mortality (%)
Influenza (INF) A/B	1.3-40	7-44	8-28
Parainfluenza (PIV)	3-27	7-50	10-50
Respiratory syncytial virus (RSV)	1-50	14-70	11-47
Human Metapneumovirus (HMPV)	2-11	5-41	6-40
Adenovirus (ADV)	1-30	14-42	14-73
Human Rhinovirus (HRV)	2-34	<5-27	<5-41
Human Coronavirus (HCoV)	3-23	<5	<5-54

Based on these data, some HCT centers in Brazil and many around the world have the testing of respiratory viruses in all candidates (symptomatic or not) before admission for transplantation as a standard of care.

The COVID-19 pandemic brought the opportunity to expand the testing recommendation also for asymptomatic candidates, due to the high transmissibility of SARS CoV-2 even in asymptomatic or pre-symptomatic cases. A systematic review and meta-analysis of 95 studies evaluating proven SARS CoV-2 infections showed a rate of 40.5% (95% CI; 33.5-47.5) of asymptomatic cases[14].

With the current decrease in COVID-19 cases in Brazil, several sectors (hospitals, transplant professionals, health plans, etc.) have been pushing to suspend the recommendation of pre-HCT testing for SARS CoV-2 in asymptomatic candidates.

However, we are still far from epidemiological stabilization of COVID-19. In August 2023, the World Health Organization (WHO) issued a statement about a new subvariant of interest (VOI) of the Omicron strain called EG.5, already identified in 51 countries. The EG.5 subvariant has new mutations that confer greater transmission capacity and immune escape, and is therefore capable of increasing the number of COVID-19 cases worldwide.

In light of this warning from the WHO, the Brazilian Society of Infectious Diseases published a technical note recommending to health authorities at the federal, state and municipal levels, measures to increase the collection of diagnostic tests and genomic surveillance of COVID-19 cases, aiming to early detection of the EG.5 subvariant[15].

In addition to the instability of the epidemiological situation of COVID-19 and the high frequency of asymptomatic infections caused by SARS CoV-2, other respiratory viruses circulate throughout the year in the community and data from Sivep-Gripe clearly show the increase in these agents when decreases the incidence of SARS CoV-2, possibly due to competition for the host. A recent epidemiological study demonstrated that the frequency of asymptomatic infections for most respiratory viruses in the general population is greater than 50%[16].

In HCT recipients, the frequency of asymptomatic infections with respiratory viruses other than SARS CoV-2 is about 23%, occurring in 14.5% of adults and more than 30% of the pediatric population[5,17,18].

Based on the above, the ideal recommendation for patient safety is not only to maintain the testing of asymptomatic patients, but also to expand the diagnostic capacity of the current assays targeting other respiratory viruses.

We understand that economic and/or logistical limitations interfere with the decision to test asymptomatic people. However, it is up to the SBTMO Infections Group to clarify the risks and define recommendations (even in an ideal scenario) that offer a greater probability of protection for patients and HCT Units. Likewise, it is up to HCT centers and Institutions to adjust these recommendations in the best possible way.

RECOMMENDATIONS FOR PREVENTION AND TESTING OF RESPIRATORY VIRUSES IN HCT UNITS

1. Healthcare professionals, HCT candidates, donors and recipients must be up to date with vaccinations against COVID-19 and influenza. Booster doses of the COVID-19 vaccine for this population must have been administered with the bivalent vaccine, and preferably less than 1 year ago. It is important to highlight that vaccines remain active in protecting severity and deaths for all circulating variants of SARS CoV-2, including EG.5[15].

2. Maintenance of non-pharmacological measures to control the transmission of respiratory viruses, that is, use of masks when indicated, social distancing, frequent hand hygiene with soap and water and/or alcohol gel, cough toilet, isolation of positive cases according to the recommended precautions, etc.

3. For the safety of HCT recipients and to reduce the risk of transmission of SARS CoV-2 and other respiratory viruses in HCT units, candidates, donors and companions must be tested for respiratory viruses before admission, regardless of the presence of respiratory symptoms.

4. Daily questioning of respiratory symptoms is mandatory for healthcare professionals, patients and companions throughout hospitalization, and during outpatient visits. Patients with symptoms should be removed from positive pressure rooms. All symptomatic patients should be tested for diagnosis of RV[13].

5. After HCT, testing of asymptomatic patients is only recommended for healthcare professionals, patients or companions who had contact in the previous week with a suspected or confirmed case of respiratory viruses.

6. The healthcare professional (symptomatic or asymptomatic) diagnosed with RV must be removed for a specified period of time in accordance with local recommendations.

7. Preferably, RV diagnosis should be made with PCR diagnostic platforms, including all respiratory viruses (multiplex). There are several multiplex PCR testing platforms available on the market. If it is impossible to use broad diagnostic platforms, customized solutions can be used, as long as they include the RVs that are known to pose a greater risk to the patient (RSV, Influenza A and B, Parainfluenza, Metapneumovirus, SARS CoV-2 and Adenovirus). ELISA tests and direct or indirect immunofluorescence tests (IFD or IFI) have good diagnostic sensitivity and specificity, although lower than molecular tests. The diagnostic targets of IF or ELISA tests are limited to include only RSV, INF A/B, PIV, and ADV.

8. Antigen tests for COVID-19 can be used in symptomatic patients, but not for screening asymptomatic individuals, as they have lower sensitivity compared to molecular tests[13]. Likewise, chromatography tests for RSV or INF A/B should not be used for diagnosis due to low sensitivity.

9. Donors who test positive for RV should be excluded from donating until full recovery from symptoms. There is no disease-free interval before transplantation considered optimal in the case of an infected donor[19]. In case of urgency for the transplant, the safest measure is to repeat the collection after 7 days and if the result is negative and the donor is asymptomatic, HCT can continue.

10. In candidates with a positive test for respiratory viruses, it is recommended to postpone the HCT. The decision to proceed with HCT must be balanced between the respiratory virus detected, the candidate's immunological status, the availability of antiviral and/or monoclonal drugs (in the case of COVID-19) that are effective in avoiding RV infection complications *versus* the risk of disease progression and the loss of remission status that will certainly affect the success of HCT. If the decision is to proceed with HCT, the candidate and/or guardian must be aware of the risks assumed by the team and authorize the transplant to be carried out.

11. In the case of candidates or recipients who have had COVID-19 and persist with a positive test for a prolonged period, the use of the PCR reaction CT above 30 cycles can be used to decide whether to admit the patient to the HCT unit (never in positive pressure rooms). In these cases, the risk of transmission is low, but not zero[13]. It is important to remember that CT >30 does not guarantee a lower risk of complications from COVID-19 after HCT.

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