

PAHPBS SARS-CoV-2/Covid-19 Vaccine Recommendations



April 2021

The Philippine Association of Hepato-pancreato-biliary Surgeons (PAHPBS) is continuously committed to serve our patients with hepatobiliary and pancreatic (HPB) diseases, including cancer, especially during these uncertain times. Last year, as the Covid-19 pandemic developed and demanded for healthcare increase, the impact was felt in every sector of every healthcare system around the world, including the cancellation of elective surgery.^{1,2} In response to the pandemic, PAHPBS released several papers on COVID-19 guidelines for liver, biliary, and pancreatic surgery.² In this update, PAHPBS aims to discuss and clarify current recommendations on – HPB diseases, Surgery, and the COVID-19 vaccine.

Just over a month ago, the Philippines rolled out the mass vaccination program against the COVID-19 virus. At least two vaccines – Sinovac and AstraZeneca, were the first to arrive in the country (among the four Philippine FDA approved vaccines).

As of April 13, 2021, a total of 1.2 million doses were administered – those given top priority in the initial roll-out were Healthcare frontline workers (A1), followed by Senior Citizens (A2), and persons with co-morbidities (A3). The goal for prioritization is to reduce mortality and preserve the healthcare capacity of the country.² The people belonging to “A3” are adults (18-59 years old) with controlled co-morbidity.³ Included in this subgroup are patients with hepatobiliary and pancreatic (HPB) diseases. While HPB disease comprise a diverse group of disease entities.

For surgical purposes, we focus on HPB tumors; most of the lesions that arise in the liver, biliary tract, and pancreas are carcinomas. Thus, surgical resection is the only potentially curative treatment option for most types of malignant HPB tumors, if the disease is resectable and limited.² However, most HPB malignancies are locally advanced or metastatic when

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Data as of March 31, 2021

	Pfizer BioNTech	Oxford AstraZeneca	Sinovac CoronaVac	Gamaleya Sputnik V	Bharat BioTech	Moderna	Novavax	Janssen
Technology Platform	mRNA	Viral Vector (non-replicating)	Inactivated Virus	Viral Vector (non-replicating)	Inactivated Virus	mRNA	Protein Subunit	Viral Vector (non-replicating)
Philippine FDA EUA Approval [A]	January 14, 2021	January 28, 2021	February 22, 2021	March 19, 2021	Applied for EUA to Philippine FDA (January 22, 2021)	-	-	Applied for EUA to Philippine FDA (March 31, 2021)
Dose and Frequency	2 doses, 21 days apart [A]	2 doses, 4-12 weeks apart [A]	2 doses, 28 days apart [A]	2 doses, 3 weeks apart [A]	2 doses, 14 days apart [C]	2 doses, 28 days apart [B]	2 doses, 21 days apart [C]	1 dose [F]
Storage Requirements	-80 to -60°C [A]	2 to 8°C [A]	2 to 8°C [A]	-18°C and below (frozen solution) [A]	2 to 8°C [B]	-25 to -15°C 2 to 8°C (30 days) [C]	2 to 8°C [H]	-20°C (2 years) 2 to 8°C (3 months) [B]
Vaccine Efficacy Based on Phase III Clinical Trial (CT)	95% against symptomatic COVID-19 [A] [B]	70.4% against symptomatic COVID-19 [A] [B] 100% against severe COVID-19 [B]	65-91% (based on Brazil, Indonesia, and Turkey Trials) [A]	91.6% against symptomatic COVID-19 [B] 100% against moderate or severe cases [B]	80.6% against PCR-confirmed symptomatic COVID-19 [B]	94.1% against symptomatic COVID-19 [B] 100% against severe COVID-19 [B]	awaiting official Phase III Interim Journal Publication	66.1-66.9% against confirmed moderate to severe/critical COVID-19 [A]
Common Adverse Events Reported in Phase III CT	• short-term, mild-to-moderate pain at the injection site, [B] • fatigue, headache [B]	• injection site pain and tenderness [B] • fatigue, headache, feverishness, myalgia [B]	• local lymphadenopathy at the injection site, [B] • allergic reaction that may be caused by any component of the vaccine (hives, allergic rashes and purpura, anaphylactic shock) [B] • convulsion (with or without fever) [B]	• pain on injection site, hyperthermia, swelling [B] • headache, asthenia, muscle/joint pain, malaise, sore throat, diarrhea, rhinorrhea, loss of appetite, pain in the oropharynx, nasal congestion, colds, sneezing, cough [B]	• headache [B] • fatigue [B] • fever [B] • body ache [B] • abdominal pain [B] • nausea [B] • vomiting [B]	• pain/erythema/swelling on injection site, axillary lymphadenopathy [B] • fever, headache, fatigue, myalgia, arthralgia, nausea, vomiting, chills [B]	awaiting official Phase III Interim Journal Publication	• injection site pain, redness, swelling [B] • tiredness, headache, muscle pain, chills, fever, nausea [B]

References: [A] FDA Philippines EUA Approval [B] Publications in Journals for Phase III Interim Results [C] WHO Landscape and Tracker of COVID-19 Candidate Vaccines [D] WHO Interim recommendations for EUA [E] Submission to FDA EUA Application [F] ClinicalTrials.gov [G] Center for Disease Control and Prevention [H] Publication in Journals for Phase 1 and/or Phase 2 CT results [I] FDA Published Product Information Materials [J] US FDA Published Vaccine Fact Sheets

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diagnosed. This means that most of the patients will undergo palliative treatment rather than cure.

Last year, there was a significant decline in HPB cases in the Philippines and around the world. In a study by Balakrishnan et al, their survey showed a significant drop in the number of HBP cancer surgery being performed and need to adopt non-operative treatment strategies, alternatives included increased neoadjuvant chemotherapy for pancreatic cancer and colorectal liver metastases, and locoregional treatments for hepatocellular carcinoma.⁴ Delaying surgery during this pandemic poses a risk of disease progression in HBP cancers, at the same time, diverting resectable cases towards chemotherapy does not completely mean decreasing risk from COVID-19, in fact, chemotherapy-induced immunosuppression may predispose the patient towards severe infection; on the other hand, a lack of response to chemotherapy would inevitably result in progressive disease.^{7,4}

Most of the International and Local Surgical Societies already set several mitigating measures (such as COVID-19 RT PCR screening, maintaining perioperative standards, case prioritization) in their guidelines for safe resumption of surgery last year. This year, another layer of protection is recommended in the form of SARS-COV-2 (COVID-19) vaccine. Several COVID-19 vaccines demonstrated 100 per cent effectiveness in preventing COVID-19-related deaths after phase III trials. Thus, new recommendations are coming out regarding vaccination and surgery. In the COVIDSurg Collaborative study that was recently published, they recommend that surgical patients, particularly those undergoing cancer surgery, should also be given priority ahead of the general population.⁴ At the same time, prioritization of vaccination for surgical patients could support safe re-initiation of elective surgical services.⁹ In addition, COVID-19 vaccination is likely to decrease postoperative pulmonary complications, reducing intensive care use and overall healthcare costs.⁹

So what does this mean for HBP surgery? Do we need to get a vaccine before a surgery? How long after surgery can we be vaccinated? These questions will be answered in this guideline.

I. GUIDELINES FOR PANCREATIC CANCER AND COVID-19 VACCINATION

Pancreatic cancer remains one of the deadliest cancers regardless of the changes brought about by the COVID-19 pandemic.¹⁰ Therefore, it is essential that pancreatic cancer patients should be given reasonable priority in receiving the COVID-19 vaccine.

Patients undergoing active chemotherapy, immunotherapy, or continuing antibody treatments for cancer or having other targeted cancer treatments that can affect the immune system should be in the reasonable priority list in receiving COVID-19 vaccine. Moreover, patients with pancreatic cancer who are 70 years old and above should be given higher priority than the younger age group since they will not necessarily be receiving treatment in the palliative stage. Individuals with malignancies in general, have a higher risk of mortality and serious Covid-19 disease.^{10,11}

The highest priority to receive the COVID-19 vaccine are those statistically most vulnerable to the virus. For patients with pancreatic cancer who are not receiving active treatment, their wait for the vaccination should be reduced. If a patient is about to start treatment

for pancreatic cancer, such as chemotherapy and some radiotherapy and steroids, vaccination should be given before starting the treatment. Ideally, vaccine should be given two weeks before the treatment, and if possible, should have completed the two doses (depending on the type of vaccine available). Surgical management should not be delayed in favor of vaccination, but a safe interval should be observed, with vaccination administered a minimum of two weeks before or after surgery; or when the surgeon has assessed patient to be recovered from surgery.

Some patients with pancreatic cancer are more at risk of becoming seriously ill if they get Covid-19. They are considered “clinically extremely vulnerable”.¹¹ These include:

1. Patients who have cancer and are having chemotherapy.
2. Patients who underwent surgical removal of the spleen (asplenia) concomitant with pancreatic surgery.
3. Patients having immunotherapy.

Patients with pancreatic cancer who are not on chemotherapy are still advised to protect themselves from Covid-19 and some patients are more at risk of getting ill if they catch SARS-CoV-2 infection. These include:

1. Patients who have completed chemotherapy
2. Patients receiving radiotherapy or chemoradiotherapy
3. Patients 70 years old and above
4. Patients with concomitant diabetes
5. Patients who have recovered from surgery

It is very important to note that a patient with pancreatic cancer should be at a high priority list to receive the vaccine.¹² After being vaccinated, standard health precautions and protocols should still be always maintained and observed strictly.

II. GUIDELINES FOR CHRONIC LIVER DISEASE, LIVER CANCER, LIVER TRANSPLANT AND COVID-19 VACCINATION

CHRONIC LIVER DISEASE

People with chronic liver disease (CLD) are at increased risk for a severe course of Covid-19; especially those with cirrhosis in advanced stages, with hepatobiliary cancer, and liver transplant patients, whether they are candidates for liver transplantation or have already undergone transplantation. A more severe course of COVID-19 translates into increased death rates, including mortality due to liver failure.

Patients with CLD have dysregulated innate and adaptive immune response; an area of particular concern may be associated with vaccine hypo-responsiveness in this subset of patients. However, there no data as to whether these patients may respond differently to the various Covid-19 vaccines. While vaccines, in general, may be less effective in patients with Chronic Liver Disease and post liver transplant, there are currently no available data specifically for the currently available Covid-19 vaccines.

While specific data on patients with CLD is limited, risks of adverse reaction from vaccination are extremely rare, likewise for patients on immunosuppressive regimens. There is

no evidence of safety concerns for people who are immunosuppressed, for both the mRNA vaccines or for the viral vector vaccine.

The following groups should be prioritized for COVID-19 vaccination¹²:

1. Patients who have advanced liver disease (compensated or decompensated cirrhosis)
2. Patients who have undergone a liver transplant
3. Patients who have hepatobiliary cancer
4. Patients with chronic liver disease and are immunosuppressed

People living with CLD with no or modest fibrosis should be vaccinated in accordance with the priorities set for the general population, considering other factors such as their age, and other potential conditions, such as living with obesity or diabetes.

The safety and efficacy of COVID-19 vaccines in children and adolescents under the age of 16 years have not yet been established. So far, as of the date of publication of this policy statement, there is no data available. Immunization policies for patients with previous exposure to COVID-19 are still undefined. However, those people who have had Covid-19, regardless of their symptoms, can probably delay vaccination until 6 months after their SARS-CoV-2 infection.

Long-term safety data on SARS-CoV-2 vaccination in patients with liver disease are not yet available; however, it is important to weigh the predicted benefit of vaccination against the potential risk of vaccination, especially given the already known serious consequences of SARS-CoV-2 infection in at-risk populations.

LIVER CANCER

Patients with Liver Cancer need special consideration and must be prioritized for vaccination, considering the risk of severe Covid-19 in this subset of patients.^{12,14,15} On one hand, these patients usually have concomitant CLD, and on the other hand, curative treatment options may be delayed in case of Covid-19 disease. There is no confirmed information yet on the tolerability, immunogenicity and safety of novel Covid-19 vaccines in patients with hepatobiliary cancer.

If a patient is about to undergo surgery or treatment for liver cancer, vaccination should be given before starting the treatment. Covidurg data has shown that ideally, at least the first dose of vaccine should be given two weeks before treatment, and if possible, should have completed the two doses (depending on the type of vaccine available). However, treatment should not be delayed. In the case of patients who have recovered from surgery, a minimum period of a 2-week interval should be observed between surgery and vaccination; or as the attending specialist has deemed the patient sufficiently recovered from surgery. Patients with liver cancer who are not receiving active treatment, should also be prioritized for vaccination.⁹

Given the high risk of serious health consequences of SARS-CoV-2 infection in patients with hepatobiliary cancer, the potential benefits of the vaccine, both to patients and to healthcare systems, are likely to outweigh the risks associated with vaccination.^{12,15}

LIVER TRANSPLANT PATIENTS

Liver transplant patients do not appear to have an increased risk of mortality following SARS-CoV-2 infection compared with the matched general population, but they do have higher rates of admission to intensive care. They could have been relatively more protected throughout the pandemic due to enhanced social distancing, a phenomenon called “shielding”.¹³

Thus, this group remains a vulnerable population and should be prioritized for vaccination, with the benefits far outweighing the potential risks.^{12,13} The value of routine immunization in liver transplant recipients is well-established, with vaccine immunogenicity greatest pre-transplantation rather than post-transplantation, even in the context of advanced liver disease.

The timing of vaccination is important, and it is recommended that vaccination should be completed prior to transplantation, ideally very early on in the course of CLD, and latest would be at the time of listing. In most circumstances, live replicating vaccinations should be avoided in immunosuppressed patients. None of the currently available Covid-19 vaccines contain live replicating virus. After transplantation, vaccination is usually not recommended within the first 3-6 months during the period of intense immunosuppression, as immune responses are expected to be decreased.

Since liver transplant recipients may not have adequate protection against vaccine-preventable diseases in the early post-transplant period due to impaired immune responses or incomplete vaccination status, we advise that household contacts of organ transplant recipients and candidates, as well as healthcare workers and care-givers at transplant centers be vaccinated against Covid-19.¹²

There is so far no confirmed information on the tolerability, reactogenicity, immunogenicity and overall safety of COVID-19 vaccines in SOT patients given the design in phase III trials

CONCLUSION

The PAHPBS recommends prompt vaccination against COVID-19 for all patients with CLD, HPB Cancers, and Liver Transplant patients. We advise vaccination of these high-priority patient populations with an FDA-approved available vaccine. Standard precautions against hypersensitivity and anaphylaxis should be observed. All patients are advised to seek consult with their specialist physicians prior to vaccination.

The best way to avoid COVID-19 still, is to always avoid exposure to SARS-CoV-2. Even after vaccination for COVID-19, we advise all patients to take steps to protect themselves and others by wearing a mask, staying 6 feet from other people in social situations, avoiding crowds and poorly ventilated spaces, and washing their hands often.

Patients should also continue to maintain a healthy lifestyle as the best way to keep the immune system healthy. All advice regarding vaccinations in this patient population must be tailored and decisions must be made upon the advice of the medical specialist or multidisciplinary team.

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