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# Hypersplenism Caused by Portal Hypertension due to Abnormal Liver Function

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**Abstract**
Portal hypertension refers to a range of complications that arise from elevated pressure in the portal vein system, which can be caused by various factors. The primary causes of portal hypertension are cirrhosis induced by viral hepatitis and non-cirrhotic factors such as Budd-Chiari syndrome, portal cavernous transformation, and regional portal hypertension. Patients with portal hypertension experience increased blood flow and resistance in the portal vein, leading to enlargement of the spleen and increased splenic function. This, in turn, can result in a decrease in blood cells and an overgrowth of bone marrow hematopoietic cells, leading to complications like anemia, bleeding, and infection. The treatment for splenomegaly induced by portal hypertension involves both medical and surgical approaches, with surgical treatment being the primary method. This article provides an overview of the common treatment options for splenomegaly caused by portal hypertension.

**Keywords:** Hypersplenism, Hypertension, Liver

## 1. Introduction

Portal hypertension is a prevalent issue, with higher rates in developing nations compared to Western European countries. The incidence is particularly high in Asia, specifically in India and Japan. Noncirrhotic portal hypertension accounts for approximately 25% of global cases, but in Japan, the number of new cases has significantly decreased to only 11 annually. In North America and Europe, NCPH is considered a rare condition, making up only 3-5% of portal hypertension cases (Dhiman et al., 2002; Sarin et al., 2007) .

The diagnosis of NCPH primarily involves ruling out other potential causes of portal hypertension and liver diseases. This includes confirming clear signs of portal hypertension, conducting appropriate serological tests, liver biopsies, and radiological examinations to exclude chronic liver diseases like viral hepatitis, fatty liver, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis (PBC), and Budd-Chiari syndrome. Portal hypertension is characterized by an increase in portal pressure (> 10 mmHg) and can be caused by liver cirrhosis or noncirrhotic diseases in portal and hepatic veins (Schouten, Garcia-Pagan, Valla, & Janssen, 2011; Schouten, Verheij, & Seijo, 2015). When portal hypertension occurs without liver cirrhosis, NCPH becomes a consideration. The prognosis for NCPH is generally more favorable than that of cirrhosis, and noncirrhotic diseases are a common

cause of portal hypertension in developing regions, especially in Asia (Rajekar, Vasishta, Chawla, & Dhiman, 2011). NCPH encompasses a wide range of diseases with origins either within or outside the liver. Typically, the lesions in NCPH are vascular and can be classified based on the location of blood flow resistance. In many cases, these conditions are associated with damage to endothelial cells, thickening of the inner lining of blood vessels, blockages due to blood clots, or scarring within the portal system of the liver effects by portal hypertension (Sarin & Kumar, 2006).

**2. Etiology of Portal hypertension**

The development of portal hypertension in humans is believed to be caused by a combination of increased resistance in the hepatic vascular bed, known as "backflow," and a hyperdynamic splanchnic circulation, referred to as the "forward flow" theory. This condition can be classified into prehepatic, intrahepatic, and posthepatic forms, each with its characteristics and contributing factors. The main cause of certain types of pre- and intrahepatic portal hypertension is an increase in splanchnic blood flow. Intrahepatic portal hypertension can be further categorized into presinusoidal, sinusoidal, or post-sinusoidal types, although not all diseases fit neatly into these classifications. The contribution of each factor to elevated portal pressure in liver cirrhosis varies depending on the underlying cause, Recent studies have focused on spleen stiffness as a potential indicator of portal hypertension, as it can be measured using non-invasive imaging techniques like transient elastography and acoustic radiation force impulse imaging. Some research suggests that spleen stiffness may predict the presence of varices or ascites in individuals with portal hypertension. In an experimental model of cirrhosis with portal hypertension, there was a positive correlation between portal pressure and spleen size, highlighting the complex factors involved in this condition (Vadlapudi et al., 2024).

**3. Risk Factors**

Portal hypertension does not have any well-defined risk factors, however, cirrhosis, which is the primary cause of portal hypertension, is associated with a multitude of risk factors. Some common risk factors that contribute to the development of cirrhosis include intravenous drug use (IVDU), tattooing or piercing in unsanitary conditions, needlestick injuries, blood transfusions before 1992, viral hepatitis infections, and engaging in unprotected sexual intercourse. These risk factors can significantly increase the likelihood of developing cirrhosis, which in turn can lead to the development of portal hypertension. It is important for individuals to be aware of these risk factors and take necessary precautions to prevent the onset of cirrhosis and subsequent complications such as portal hypertension (Metwally, Essam, Atwa, Awad, & Abdelsameea, 2022).

**4. Pathophysiology of Portal hypertension**

The main cause of portal hypertension in cirrhosis is an increase in resistance to blood flow within the liver. This resistance is primarily due to structural changes associated with fibrosis/cirrhosis and constriction of blood vessels within the liver. Research has shown that vasoconstriction within the liver alone accounts for at least 25% of the overall increase in resistance. It is important to note that changes in certain types of liver cells, such as hepatic stellate cells and liver sinusoidal endothelial cells, play a crucial role in increasing resistance and have been extensively studied. Once portal hypertension develops, collateral vessels form as alternative pathways for blood from the digestive organs. However, these vessels also contribute to an increase in blood flow within the portal vein, worsening the already elevated portal hypertension. Additionally, cirrhosis is characterized by dilation of arteries in both the splanchnic and systemic circulations, further increasing blood flow to the portal vein. Therefore, simply reducing the formation of collateral vessels would not effectively alleviate portal hypertension. It is crucial to inhibit arterial dilation in the splanchnic circulation to decrease blood flow to the portal vein. This combined approach is essential in the treatment of portal hypertension. This section provides a detailed analysis of the mechanisms underlying the formation of collateral vessels and arterial dilation in the splanchnic and systemic circulations in cirrhosis with portal hypertension (Buob, Johnston, & Webster, 2011; Iwakiri, 2014).

## 5. Complication of Portal hypertension

Internal bleeding can be a severe consequence of esophageal varices, which are enlarged veins located at the lower end of the esophagus. These varices develop due to portal hypertension, where blood flow is obstructed in nearby veins in the esophagus and stomach. When varices burst, they can lead to life-threatening internal bleeding, particularly at the junction of the esophagus and stomach, resulting in sudden and forceful vomiting of blood. In addition to the risk of internal bleeding, individuals with esophageal varices may also experience fluid buildup in the stomach, leading to feelings of fullness, rapid weight loss, and malnutrition. The accumulation of fluid can cause discomfort and hinder mobility, as the pressure on the diaphragm may result in breathing difficulties. These symptoms can significantly impact the quality of life for affected individuals. Furthermore, complications associated with esophageal varices can extend to kidney and lung problems, further exacerbating the health risks posed by this condition. Kidney problems may arise due to the body's inability to effectively regulate fluid levels, while lung problems can occur as a result of pressure exerted by the accumulated fluid. These additional health issues underscore the seriousness of esophageal varices and the importance of timely medical intervention to manage and treat this condition effectively (Simonetto, Liu, & Kamath, 2019).

## 6. Treatment Strategies

The initial approach to managing hepatopulmonary syndrome involves the administration of oxygen therapy, while hepatorenal syndrome is typically treated with dialysis. Hepatic encephalopathy is addressed through the use of specific medications, and excess fluid from ascites is removed via paracentesis, which also allows for testing for peritonitis. In cases where there is a need to redirect blood flow through the portal venous system and alleviate pressure, two different shunt procedures may be considered. These procedures aim to provide relief by altering the circulation of blood within the body. Treatment options for portal hypertension-induced splenomegaly are somewhat limited within the realm of internal medicine. The focus is primarily on managing the underlying condition and providing symptomatic relief. Antiviral therapy is often recommended for patients with liver cirrhosis resulting from viral hepatitis B, as it can help improve liver function and reduce liver fibrosis, ultimately easing symptoms associated with hypersplenism (Li et al., 2017). However, when patients with cirrhosis following hepatitis C receive interferon therapy, it can further decrease their white blood cell and overall blood cell count. In addition to treating the underlying disease, there are various methods that can be used to reduce blood cell count. Common treatments include infusing blood products, using erythropoietin, recombinant human granulocyte colony-stimulating factor, recombinant human thrombopoietin, and administering platelet-raising capsules to stimulate blood cell production. Furthermore, certain medications have shown positive therapeutic effects in treating splenomegaly caused by portal hypertension. These medications include those that clear and remove blood stasis, improve blood circulation, and unblock collaterals, among others. The choice of these medications should be based on clinical considerations (Pozzato, Marzano, Botta, Anania, & Uslenghi, 1998).

Following a comprehensive internal medicine treatment, early splenic hyperactivity can be relieved without resorting to surgical intervention if the root cause can be effectively managed. However, in cases where the primary disease treatment fails to yield satisfactory results, the spleen may experience significant compression from neighboring organs, leading to severe bleeding and posing challenges for treatment. In such instances, surgical treatment is advised to control recurrent infections and mitigate severe damage to blood cells (Merkel, Gatta, Arnaboldi, & Zuin, 1985; Yoshida et al., 2023).

## 7. Surgical Treatment

Splenectomy is typically recommended when other treatment options have failed to provide relief or when the enlarged spleen is causing severe symptoms such as pain, anemia, or low platelet count. The surgery can be performed through open surgery or laparoscopic techniques, depending on the individual's specific condition and overall health. During a splenectomy, the surgeon carefully removes the spleen while taking care to preserve surrounding organs and tissues. After the surgery, patients may experience some discomfort and require a period of recovery before returning to normal activities. It is important for individuals who have undergone a splenectomy to receive vaccinations against certain infections, as the spleen plays a crucial role in the immune system's response

to bacteria and viruses. While splenectomy can effectively treat splenomegaly and its associated symptoms, Overall, splenectomy remains a valuable option for individuals with severe splenomegaly who have not responded to other forms of treatment (Al-raimi & Zheng, 2016).

**8. Complete splenectomy**

Splenomegaly, or an enlarged spleen, can be effectively treated through complete splenectomy. This treatment approach encompasses various methods, including traditional open splenectomy, laparoscopic splenectomy, and da Vinci robot-assisted splenectomy. Over time, these procedures have become more standardized, particularly the traditional open splenectomy, which is now commonly performed in local hospitals worldwide. In cases where patients have both portal hypertension and splenomegaly, splenectomy is often accompanied by additional procedures such as periportal vascular dissection or portal body shunting. These additional measures, such as splenic cavity and splenic kidney shunting, are implemented to prevent and manage upper gastrointestinal bleeding (Miko et al., 2017). Emphasizing the importance of removing any potential accessory spleen during a splenectomy is crucial to prevent splenomegaly recurrence post-surgery. However, there is a risk of OPSI after complete spleen removal, so it is recommended to avoid this in adolescent patients with immature immune systems if possible. Complications such as portal vein thrombosis and abdominal fluid accumulation can occur after a splenectomy, highlighting the need for careful consideration and risk assessment before proceeding with the procedure.

Laparoscopic and robot-assisted splenectomies offer advantages over traditional open surgery, including reduced trauma, less blood loss, shorter hospital stays, and lower complication rates. As a result, these techniques are becoming increasingly popular in the field of splenectomy (Morgan & Tomich, 2012).

**9. Partial splenectomy**

Scholars have made significant advancements in understanding the role of the spleen, leading to a widespread agreement within the medical community to minimize the risk of developing overwhelming post-splenectomy infection (OPSI) (Sinwar, 2014). Therefore, it is crucial to prioritize the preservation of splenic function by utilizing various methods such as regular partial splenectomy and autologous splenic transplantation. Recent studies have shown that the spleen, similar to the liver, has distinct blood supply segments and avascular zones between them. This understanding of the spleen's anatomy serves as the foundation for regular partial splenectomy, which involves removing specific portions of the spleen based on the distribution pattern of blood vessels.

It may choose to perform splenectomy (complete removal of the spleen), lobectomy (removal of a lobe), or hemisplenectomy (removal of half of the spleen) depending on the distribution of blood vessels. These surgical techniques aim to preserve the essential functions of the spleen while addressing specific medical conditions or injuries (Zouki & Fry, 2024). However, the widespread adoption of partial splenectomy is hindered by the challenge of accurately identifying blood vessel distribution in the spleen during surgery. This procedure, compared to complete splenectomy, presents difficulties in controlling bleeding and carries a higher risk of postoperative bleeding. These factors contribute to the limited use of partial splenectomy due to the associated risks and complexities involved. To address the limitations of partial splenectomy and the potential decrease in immune function, experts suggest autologous splenic transplantation. This involves transplanting healthy splenic tissue into different areas of the body, such as the omental sac, splenic bed, and retroperitoneum. Various techniques, including semi splenic transplantation with a vascular pedicle, splenic slice transplantation, and splenic cell transplantation, can be utilized for autologous splenic transplantation. Research indicates that autologous splenic transplantation has the potential to partially preserve the immune function of the spleen. However, further investigation is needed to fully understand the effectiveness and implications of this transplantation method. By examining the advantages and limitations of autologous splenic transplantation, researchers can contribute to improved surgical outcomes and enhanced patient care in cases where splenectomy is necessary (Y. Zhang et al., 2024). It is important to highlight that when dealing with patients who have splenomegaly caused by portal hypertension, the treatment objective should not solely focus on reducing the enlargement of the spleen. It is equally crucial to consider the prevention and management of upper gastrointestinal bleeding as part of the overall treatment plan (Chaouch et al., 2024). In the case of patients with portal hypertension induced hypersplenism,

blindly performing partial splenectomy and autologous splenic transplantation may provide short-term relief from splenomegaly. However, it is important to note that this approach does not completely address the issue as residual splenic tissue can still develop splenomegaly over time. Moreover, the resulting splenic hyperdynamic circulation can further worsen portal hypertension. Therefore, it is crucial to exercise caution and carefully select the appropriate candidates for partial splenectomy, excluding adolescents and individuals with underdeveloped immune function, in order to effectively manage portal hypertension and its associated complications (Cianci et al., 2016).

**10. Spleen lung fixation surgery**

It is suggested by Japanese researchers Akita et al., the technique of spleen lung fixation surgery emerged as a potential surgical intervention for the management of Budd-Chiari syndrome (Akita & Sakoda, 1980). Our facility has implemented enhancements to a procedure referred to as modified spleen lung fixation surgery, a technique that has gained popularity in treating different forms of portal hypertension. This surgical method hinges on establishing collateral circulation between the spleen and lungs using the patient's own blood vessels to alleviate pressure in the portal vein and avert gastrointestinal hemorrhaging by incorporating splenic artery ligation and partial splenectomy into the surgical process, there is a notable improvement in reducing splenomegaly to a certain extent. These modifications have proven to be effective in enhancing the overall outcome of the surgery and in addressing the complications associated with portal hypertension (Bell-Allen, McNamara, Bull, Lewin, & O'Rourke, 2024). The recent clinical study revealed that patients suffering from portal hypertension experienced a notable rise in white blood cell count, hemoglobin levels, and platelet count twelve months post undergoing a modified splenic pulmonary fixation surgery, effectively alleviating their splenic hyperfunction. However, the primary objective of enhancing spleen lung fixation surgery is to mitigate portal hypertension and lower the chances of gastrointestinal bleeding, despite the relatively high risks associated with this procedure. It is crucial to meticulously adhere to the indications and contraindications, as opting for this surgery solely to address splenomegaly may not be a prudent decision (Merchant & Kotawala, 2024).

**11. Partial splenic embolization**

Partial splenic embolization (PSE) is a procedure that involves using vascular intervention to block specific branches of the splenic artery, leading to partial ischemic necrosis of the spleen. This results in a decrease in splenic volume and blood flow, ultimately reducing splenic function.

The main objective of partial splenic embolization is to address the decrease in white blood cells and platelets seen in conditions like liver cirrhosis and splenomegaly. By reducing splenic function through embolization, PSE aims to improve blood cell counts and alleviate symptoms associated with these medical conditions by strategically blocking branches of the splenic artery, partial splenic embolization provides a long-term treatment option for individuals with liver cirrhosis and splenomegaly. By decreasing spleen function, PSE can help manage complications and enhance quality of life for these patients in the future (Ozturk et al., 2016). Studies have indicated that pharmacological splenic embolization (PSE) has the potential to not just alleviate splenomegaly in individuals diagnosed with liver cirrhosis, but also lower portal vein pressure, mitigate the risk of upper gastrointestinal bleeding, and exhibit minimal negative impacts on liver function (Liu et al., 2024). The splenic embolism plays a crucial role in determining the therapeutic effect of PSE. Therefore, the key to achieving successful outcomes lies in effectively controlling the area of embolism. Studies have shown that when the embolic area exceeds 30%, there is a noticeable and significant increase in platelet levels in the short term. This highlights the importance of carefully managing the extent of embolism to maximize the desired therapeutic effects of PSE (Talwar et al., 2020). In order to ensure the prolonged efficacy of splenic embolization, it is crucial that the embolic area exceeds 50%. Studies have shown that when the embolic area surpasses 70%, there is a notable rise in the occurrence of postoperative complications. As a result, experts suggest maintaining the embolic area within the range of 50% to 70% to optimize outcomes and minimize risks associated with the procedure (Ahuja, Farsad, & Chadha, 2015). In Cai Mingyue et al. (Cai et al., 2016) discovered that various factors such as embolism proportion, non-infarcted spleen volume, and cholinesterase level play crucial roles in determining the effectiveness of partial splenic embolization (PSE) in treating thrombocytopenia resulting from liver cirrhosis and

splenomegaly to optimize treatment outcomes and minimize potential complications, a strategic approach involving staged and repeated splenic embolization procedures can be implemented to gradually reduce the size of the spleen. In recent years, PSE has emerged as a promising therapeutic option for managing severe splenomegaly and upper gastrointestinal bleeding associated with portal hypertension. Clinical evidence supports the safety and efficacy of PSE, positioning it as a viable alternative to surgical splenectomy in certain cases (Ueda et al., 2023).

Radiofrequency ablation (RFA) induces necrosis in local tissue by utilizing radiofrequency current, with splenic RFA specifically targeting splenic tissue to decrease splenic volume and alleviate splenomegaly. This is achieved through the combination of central region coagulation necrosis and surrounding tissue infarction, resulting in the desired therapeutic outcomes for patients with splenic-related conditions (Putnik & Ilic, 2023). Microwave ablation is primarily a method that utilizes microwave magnetic fields to desiccate and coagulate tissues. Studies have indicated that percutaneous microwave ablation plays a crucial role in enhancing white blood cells and platelets in individuals suffering from splenomegaly. The process involves the application of microwave energy to the targeted tissue, leading to the destruction of abnormal cells through heat generation. This technique has shown promising results in the treatment of various medical conditions, including liver tumors and renal cell carcinoma by utilizing microwave ablation, medical professionals can precisely target specific areas within the body, minimizing damage to surrounding healthy tissues. This minimally invasive procedure offers patients a faster recovery time and reduced risk of complications compared to traditional surgical methods (Beermann, Delle, Magnusson, & Casswall, 2021). However, it is crucial to recognize that both RFA and microwave ablation therapy pose a risk of splenic rupture and bleeding. This risk is heightened by the fragile nature of spleen tissue and the hemodynamic characteristics of the spleen, which undergoes significant circulation changes during portal hypertension. Therefore, it is essential to proceed with caution and closely monitor for these potential complications throughout the puncture procedure and beyond (Assal et al., 2017; Martins et al., 2015).

**12. Combine Therapy**

A technique known as high intensity focused ultrasound (HIFU), low-energy ultrasound is concentrated on specific tissue by means of an ultrasound focusing transducer. This concentrated ultrasound generates a thermal effect that rapidly elevates the temperature of the targeted tissue, resulting in coagulation and necrosis within the focal region. In comparison to other treatment methods such as radiofrequency ablation (RFA) and microwave ablation, HIFU offers a non-invasive approach to treating various conditions (X. Zhang et al., 2022). Studies have indicated that HIFU (High-Intensity Focused Ultrasound) demonstrates both safety and efficacy in the treatment of splenomegaly, particularly in elderly individuals with compromised liver function or underlying health conditions. Nevertheless, the precision of ultrasound ablation can be influenced by variables like focusing accuracy and respiratory movements, thereby limiting its application in the context of splenomegaly to an exploratory phase. The effectiveness and safety of this treatment modality necessitate further investigation through the lens of evidence-based medicine (Zhu et al., 2014).

The sensitivity of splenic tissue to radiation can lead to degeneration, necrosis, and fibrosis of spleen cells when local radiotherapy is used, resulting in a decrease in spleen volume and function. This can provide relief from splenomegaly, with studies showing that local radiotherapy has a similar therapeutic effect on splenomegaly induced by portal hypertension as interventional surgery. It effectively reduces blood cell levels and minimizes adverse reactions and treatment costs for patients. Another method for treating splenic hypertrophy is through percutaneous local injection of anhydrous ethanol into the spleen, which can help reduce splenic hyperactivity by inducing bacterial necrosis and fibrosis. However, like local radiotherapy, the use of anhydrous ethanol injection poses challenges due to limited clinical research. The safety and effectiveness of this treatment method require further investigation, emphasizing the importance of caution and careful consideration when choosing treatment options in clinical practice (Bolognesi, Merkel, Sacerdoti, Nava, & Gatta, 2002).

**13. Transjugular intrahepatic portosystemic shunt (TIPS)**

The procedure called Transjugular intrahepatic portosystemic shunt (TIPS) involves the use of X-ray imaging to guide an interventional radiologist in placing a stent in the liver. This method is considered less invasive than open surgery, making it a safer option for patients with specific liver conditions during the TIPS procedure, a pathway is created in the liver using a needle, allowing the doctor to connect the portal vein to one of the hepatic veins. This connection helps redirect blood flow in the liver, reducing pressure in the portal vein and improving overall liver function to ensure the pathway remains open and functional, a stent is carefully inserted and positioned by the interventional radiologist. The stent helps maintain the openness of the pathway, allowing for continuous blood flow between the portal vein and hepatic veins, Although TIPS is generally effective in managing certain liver conditions, there is a small risk of stent malfunction over time. If the stent becomes blocked or displaced, additional interventions may be necessary to address the issue and restore proper blood flow in the liver (Yu, Rao, Fergus, Lorenz, & Zangan, 2024).

**14. Distal splenorenal shunt (DSRS)**

The distal splenorenal shunt (DSRS) is a surgical intervention that could potentially offer a superior option for certain individuals. It is essential for patients to meet specific health criteria to ensure a safe surgery and recovery process, but the long-term benefits of disease management may outweigh the risks. By rerouting the splenic vein away from the liver and redirecting it to the left kidney vein, the procedure effectively decreases blood flow and pressure in both the liver and spleen, potentially leading to improved health outcomes (Rehman & Nazir, 2019).

**15. Conclusion**

The management of splenomegaly caused by portal hypertension is increasingly using techniques like radiofrequency ablation, microwave ablation, and high-intensity focused ultrasound due to advancements in research and technology. These methods have shown promising outcomes and potential for future use as minimally invasive treatments. Traditional surgical and internal medicine approaches still play a significant role, and a personalized approach is important for each patient. Portal hypertension is commonly seen in patients with cirrhotic alcoholic fatty liver disease or non-alcoholic fatty liver disease. However, evidence suggests that it can also develop in non-cirrhotic NAFLD patients. The primary cause is an increase in intrahepatic vascular resistance due to fibrosis and microcirculation damage. The diagnostic method HVPG may underestimate portal pressure in NAFLD patients, and some may experience liver decompensation even with an HVPG below the traditional threshold. Obesity can affect the accuracy of LSM in diagnosing portal hypertension.

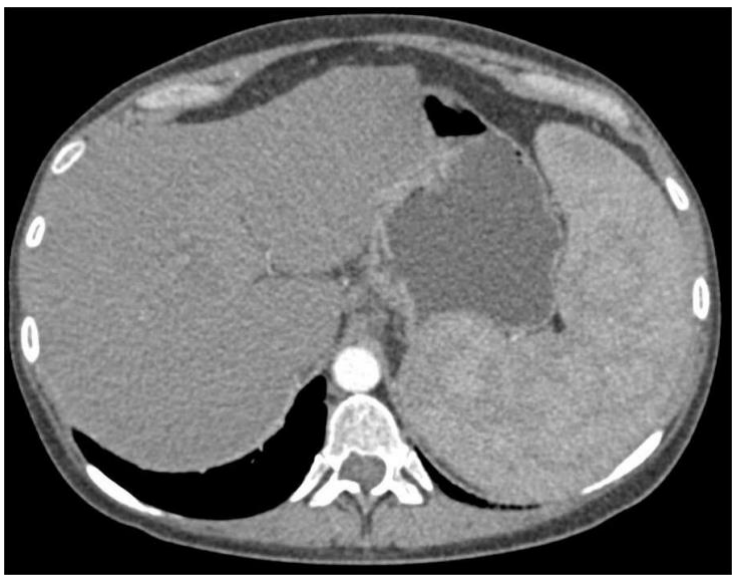

Figure 1: Hypersplenism due to portal hypertension

In figure 1 CT scan showed the hypersplenism due to portal hypertension.

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# Ending the Epidemic of Malaria in Nigeria Towards Attaining SDG Target 3.3.3: A Systematic Review of the Progress in Intervention Coverage

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**Abstract**
Background: Meeting SDG 3, 'healthy lives and well-being for all,' is one of the bedeviling challenges of low-/medium income countries like Nigeria whose health index is adversely impacted by the burden of malaria, an epidemic that seems to have defied all interventions aimed at eliminating it and achieving the SDG target. A confounding problem in the efforts so far is the apparent inability to expand and sustain interventions coverage. This review systematically examines available evidence to determine if the current level of malaria intervention coverage in Nigeria could help achieve the SDG target 3.3.3. Methods: Data were systematically extracted through online search of ProQuest databases and BioMed Central website for publication between 1st January 2015 and 3rd February 2024. Of the 26 potential articles that met the inclusion criteria, 12 were selected for quality assessment using the CASP checklist. Seven of the studies reported coverage for seasonal malaria chemoprevention (SMC), while coverage for insecticide-treated nets (ITNs) or long-lasting insecticide-treated nets (LLINs) interventions was reported by 6 of the publications. One study each reported coverage for indoor-residual spraying (IRS) and rapid diagnostic tests (RDTs). The findings were thematically discussed. Findings: The included studies were 1 systematic review (SR), 7 randomized controlled trials (RCTs) and 4 household or community campaigns/surveys. Apart from one study, all the others raised questions of external validity due to the small sample size. The descriptive statistics of the evidence showed that the mean intervention coverages for SMC, ITNs/LLINs, IRS, and RDTs, were 40.31%, 50.02%, 51.1% and 39.67%, respectively. Conclusion: The current intervention coverage is not adequate to meet the National Malaria Elimination Programme (NMEP) vision/goal of 0:10:5:80:80 and the SDG targets 3.3.3 set for the elimination of malaria by 2025 and 2030, respectively. An incremental minimum annual coverage of about 6.3% is needed over the next 6 years to meet 80% coverage for SMC. The same trajectory is estimated for other intervention components.

**Keywords:** Malaria, Epidemic, SDG Target 3.3.3, Intervention Coverage, Nigerian NMEP

## 1. Introduction

The Sustainable Development Goals (SDGs) were proclaimed in 2015 by the United Nations General Assembly (UNGA) in a resolve to improve the collective human development index (HDI) within a sustainable environment and climate while promoting equity and equality. Health is a human right and hence Goal 3 of the SDG is targeted at ensuring good health and well-being of all (INGEV, 2019; Pendar *et al.*, 2020). SDG goal 3, "to ensure healthy lives and promote well-being for all at all ages," primarily focuses on improving reproductive, maternal, neonatal and child's health (RMNCH); communicable diseases primarily Malaria, TB and HIV/AIDS; and noncommunicable diseases including cardiovascular diseases and diabetes, through a complex and intricate matrix of healthcare interventions and reducing inequities and inequalities across multiple social sectors which impact healthcare access and delivery (De Neve and Sachs, 2020).

In Nigeria, lower medium-income country, where about 39.1% live in monetary poverty and about 47.3% live in multidimensional poverty, communicable diseases especially malaria, tuberculosis, and HIV/AIDS are responsible for high disease burden, and pose a difficult challenge for SDG goal 3 (Abdulrahman, 2023; IBRD and WB, 2022). Recognizing this high burden, the country's authorities instituted several programmes and interventions toward tackling the problems of communicable diseases and meeting the SDG targets. For instance, the NMEP set up to tackle the epidemic of malaria (OSSAP-SDG and UNICEF, 2022). While there seemed to be a general improvement and decline in the prevalence data for some of these diseases, realizing the SDG target 3.3 – "end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases," remains a mystifying dream due to the protracted challenge of malaria epidemic, giving room for serious concern on the feasibility of meeting the SDG target 3.3.3 aimed at eliminating malaria from endemic countries like Nigeria.

Malaria remains a leading contributor to the global burden of diseases with estimated cases and death toll of 249 million and 608,000 in 2022, and 247 million and 619,000 in 2021 (WHO, 2023a). The SDG target 3.3.3 aims to "reduce malaria case incidence by at least 90%; reduce malaria mortality rates by at least 90%; eliminating malaria in at least 35 countries by 2030; preventing a resurgence of malaria in all countries that are malaria-free" (WHO, 2023a,b; OSSAP-SDG and UNICEF, 2022). Malaria is a hyperepidemic disease in Nigeria, and nearly everyone (97%) is at risk of the infection. The World Malaria Report 2023 showed that Nigeria contributed 27% and 31% to global incidents and deaths, respectively, making her the leading global contributor to the disease burden (WHO, 2023a). The 2018 Nigeria Demographic and Health Survey (NDHS) estimates the prevalence of malaria parasitaemia in children under-five as 23% (a decrease from 27% in 2015), and a mortality rate of 132 per 1000 live birth. Socioeconomic difference in malaria prevalence reveals a prevalence ranging from 16% in the South-South and South-East Zones to 34% in the North-West Zone; and a rural and urban prevalence of 31% and 13%, respectively (PMI, 2022, p. 13). Malaria is mostly responsible for the huge loss of work days and manhours among the country's working population. Evidence suggests that Malaria prevalence runs alongside poverty and underdevelopment (RBM Partnership and UNOPS, 2021).

Eliminating Malaria is a public health priority in Nigeria. Several strategies have been activated in the fight against malaria over the past two decades to varying degrees of success and effectiveness. Some of these strategies include SMC and/or mass administration of medicines including Intermittent Preventive Treatment in Pregnancy (IPTp); and vector control measures such as the use of ITNs and/or LLINs, IRS; and Larva Source Management (LSM) (Omojuyigbe *et al.*, 2023). The Nigerian NMEP with a vision of a malaria-free Nigeria, has a goal to attain a parasite prevalence <10% and malaria-related mortality of <50 deaths per 1,000 live births by 2025. Its primary intervention objectives include to "improve access and utilization of vector control interventions to at least 80% of targeted population by 2025" and to "ensure the provision of chemoprevention, diagnosis and appropriate treatment for 80% of the target populations at risk by 2025" (NMEP, 2024). The vision and goals of NMEP which is zero malaria, <10 parasite prevalence, <50% malaria-related deaths per 1000 live births, 80% vector control intervention access/utilization, and provision of chemoprevention/diagnosis/treatment to 80% of the population, could be summarized as 0:10:5:80:80. This vision/goals have two key intervention coverage targets of 80% of the population. The primary challenges of malaria elimination programmes have been identified as intervention coverage, and adherence to treatment, and sustainability of programme through funding and availability of

materials (Haileselassi *et al.*, 2023). For instance, ITNs ownership in Nigeria seems to have reached its crescendo with households' access to ITNs reduced from 50% in 2016 to 47% in 2018 (Omojuyigbe *et al.*, 2023). Only about two-thirds of the states regularly undertake mass campaigns for ITN use every three years, and only about 13.8% of cases are being tested. The final intervention evaluation report by MEASURE Evaluation, US-President's Malaria Initiative (PMI) in 2017 also indicates palpable gaps in household access to ITNs, IPTp and RDTs and SMC, as well as the availability of all essential commodities at health facilities (PMI, 2017). A 90% reduction on the 2015 baseline data means reducing parasitemia and prevalence to 4.5% and 2.7% respectively in children under-five. Considering this low intervention coverage for ITN, diagnosis and treatment against the set target of 80% by NMEP, there is much ground to cover to meet the SDG target 3.3.3 (Omojuyigbe *et al.*, 2023).

It is against this milieu that the research question, "is there any evidence that the current level of malaria intervention coverage can help reduce malaria case incidence and mortality by 90% each in Nigeria by the year 2030", has become very pertinent. Using the population, exposure and outcome (PEO) model, the research question was framed to carefully attempt to examine the people living in Nigeria's geographic location as the population; malaria control measures directly targeted at parasite and vector elimination as the exposure; and the coverage of intervention or its effect on parasite prevalence as the targeted outcome.

This systematic review aims to evaluate the available evidence on malaria intervention coverage with the view of assessing the possibility of meeting the SDG 3.3.3 targets based on the current trends. The review will attempt to discuss the validity and reliability of evidence and provide evidenced-based interpretations that could guide public health policy and practice in the field of malaria research and interventions, specifically, on the coverage of SMC and vector control measures. Coverage under this context will be taken as the proportion of the participants that completed the treatment regimen or the intervention programme as predetermined by the investigators.

## 2. Methods

### *2.1. Search Process*

Keywords and phrases relating to the research question were searched in online ProQuest databases (British Nursing database and ProQuest Central databases) and BioMed Central (BMC) journal website. Boolean (OR, AND, NOT), truncation and wildcard searching (*, ?, #), and phrase searching were conducted based on ProQuest databases using keywords and phrase including from malaria interventions coverage in Nigeria and intervention commodities or programmes like "antimalaria drug", SMC, INTs, IRS, RDTs, etc. The phrase used in the BMC journal website search was "Malaria intervention coverage in Nigeria." Initial searches based on titles were screened based on the inclusion/exclusion criteria to arrive at the articles included in the final analysis, as depicted in the PRISMA flow diagram in Figure 1 (Page *et al.*, 2021). The included articles were assessed for quality of evidence using information from the full texts including author, year of publication, title and aim of study, intervention, comparator, main findings, and coverage.

### *2.2. Inclusion criteria*

i. Studies/interventions conducted between 1st January 2015 and 3rd February 2024 in Nigeria.
ii. Systematic reviews and meta-analysis
iii. Randomized controlled trials/study design
iv. household clusters and intervention campaigns
v. Peer-reviewed publications

### *2.3. Exclusion criteria*

i. Studies that were not conducted in Nigeria or on Nigerians as the targeted population.
ii. Studies/interventions conducted before 2015.
iii. Studies that do not contain parasite control or vector control intervention.
iv. Studies that did not report coverage of the intervention.

v. Protocols and scoping reviews.
vi. Publications not in English Language

*2.4. Databases and website search:*

a) British Nursing Database (BND)
b) ProQuest Central Databases (PQCD)
   i. Health & Medical Collection Database
   ii. Healthcare Administration Database
   iii. Nursing & Allied Health Database
   iv. Public Health Database
c) BioMed Central (BMC) Malaria Journal website.

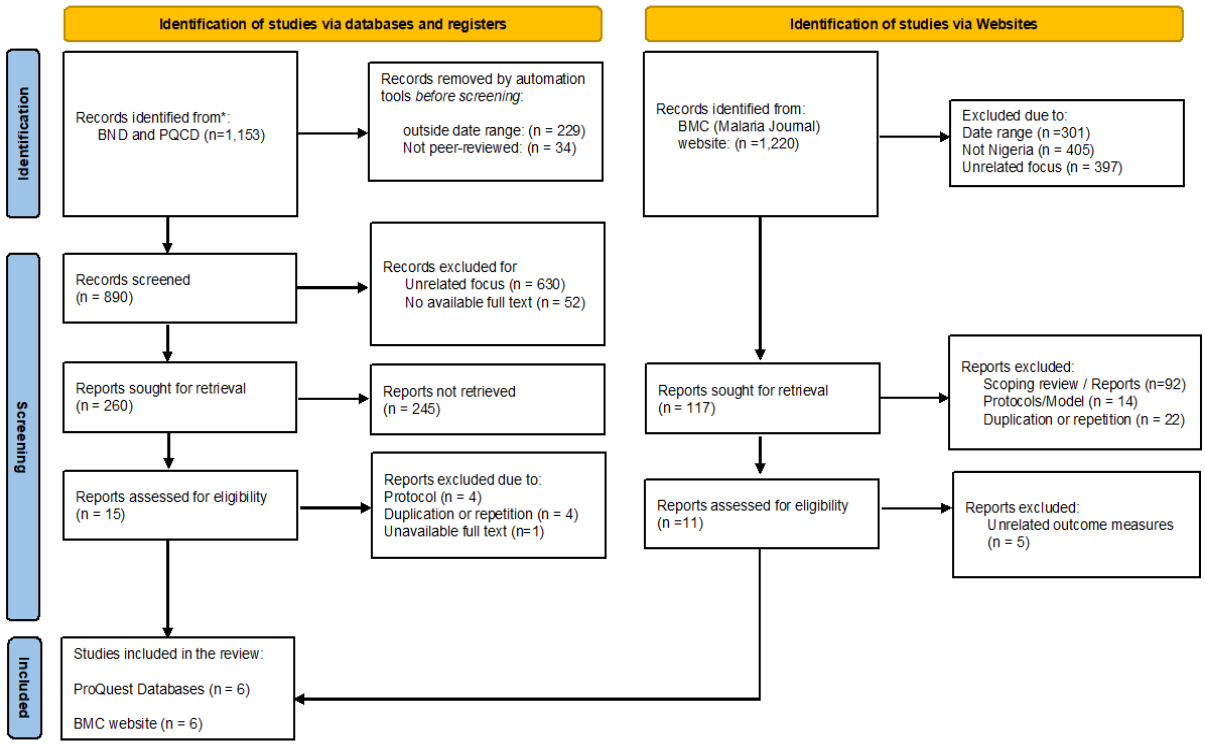


Figure 1: PRISMA flow diagram for the systematic search for evidence. Databases include BND = British Nursing Database (ProQuest), PQCD = ProQuest Central Databases, and BMC = BioMed Central at: https://malariajournal.biomedcentral.com/articles/10.1186/s12936-017-2019-1

*2.5. Method of assessment of included evidence*

The included articles were critically assessed for quality of evidence using Critical Appraisal Skills Programme checklist (CASP, 2024). Attention was paid to the aims, study design, randomization and blinding, sample size, and power, statistical inclusion of all participants, the similarity of baseline characteristics of participants, equality in groups treatment outside intervention treatment, treatment effect, conformity of outcome and conclusion, and the probable biases (see Table 1). Meta-analysis could not be conducted due to the limited number of evidence. However, descriptive statistics was used to determine mean coverage for each intervention category. An attempt was made to discuss and project the current trend, to determine the level of efforts needed in subsequent interventions to attain the SDG target 3.3.3.

Table 1: Assessment of evidence included in the study

| **Author and date** | **Title of study** | **Aim** | **Intervention** | **Comparator** | **Main finding** | **Outcome of interest to this review (*Coverage)** | **Assessment of evidence using (Critical Appraisal Skills Programme (CASP)** | | |
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| | | | | | | | **Strength in Evidence** | **Weakness/ Biases** | **Limitation /validity** |
| Falade *et al.* (2023) | "Efficacy and safety of pyronaridine artesunate versus artemether–lumefantrine in the treatment of acute uncomplicated malaria …" | "To compare the safety and efficacy of PA and AL in children aged 3 months to 12 years …" | Pyronaridine–artesunate (PA) | Artemether–lumefantrine (AL) | PA and AL were well-tolerated. PA was significantly more efficacious than AL | 95.9% | Randomized, controlled clinical trial<br><br>Outcome supported conclusion.<br><br>Defined population, and inclusion/ exclusion criteria<br><br>Clearly defined endpoint.<br><br>Balances population baseline characteristics<br><br>Sample size powered at 90%.<br><br>Appropriate statistical analysis. | Open-labeled RCT study design,<br><br>Small sample size.<br><br>Reporting bias. | Small sample size<br><br>Imbalance in age group enrolment<br><br>Low external validity |
| Hetzel *et al.* (2023) | "Pre-referral rectal artesunate: no cure for unhealthy systems" | "To understand the challenges involved in the successful real-world implementation of pre-referral rectal Artesunate…" | Pre-referrer Rectal artesunate suppositories | none | Pre-referral rectal artesunate did not increase the chance of child survival in routine clinical practice | 52% | Large sample size.<br><br>Observational study design. | Not RCT study design.<br><br>Methodical limitation in diagnosis or ailment.<br><br>Internal and External validity may be poor due to influence of access to case management. | Confounding ailments were not be properly diagnosed or defined.<br><br>Influence of quality of and access to case management and health workers adherence to guideline may have affected outcomes. |
| Okoro *et al.* (2023) | "Superiority trial of intermittent treatment with dihydroartemisinin–piperaquine versus sulfadoxine–pyrimethamine for the prevention of malaria during pregnancy" | To assess the efficacy and safety of IPTp with DP as an alternative to IPTp with SP | dihydroartemisinin–piperaquine (DP) | sulfadoxine–pyrimethamine (SP) | The risk of adverse birth outcome was not significantly different (No superiority) | 33.6% | Double-blind experimental RCT study design.<br><br>Defined Population, inclusion and exclusion criteria.<br><br>Appropriate statistical analysis | Small sample size.<br><br>Low adherence to treatment | External validity is poor due to the proportion completed treatment |

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| | | | | | | | with Cofounders adjusted for.<br><br>Statistical power 80% Outcome supported conclusion | | |
| Balami *et al.* (2021) | "Improving malaria preventive practices and pregnancy outcomes through a health education intervention…." | "To determine the effects of a malaria health educational intervention based on the information-motivation behavioural skills (IMB) model…" | A four-hour health education intervention on malaria intervention in Hausa language. | Similarly designed health education on breastfeeding | intervention was effective in improving ITN use, IPTp uptake, and haematocrit levels. | 71.77% completed the study.<br><br>*ITN = 22% (almost always use)<br><br>*IPTp = 14.65% (Completed three doses) | Double blinded randomized controlled parallel-group study<br><br>Sample size determined at 80% statistical power<br><br>Clearly defined inclusion/ exclusion criteria | Small sample size<br><br>Unclear and undetailed statistics<br><br>Self-reporting questionnaire method prone to reporting bias.<br><br>Not clear if outcome certainly reflect conclusion | Low external validity due to small sample size.<br><br>Confounding not clearly identified |
| Noguchi *et al.* (2020) | "Effect of group versus individual antenatal care on uptake of intermittent prophylactic treatment of malaria in pregnancy…" | "To determine whether women randomized to group-antenatal care (G-ANC) versus standard antenatal care (ANC) differed in IPTp uptake and insecticide-treated nets (ITN) use" | Group antenatal care (G-ANC)<br><br>IPTp uptake | Standard ANC<br><br>insecticide-treated nets (ITN) use | G-ANC may support IPTp uptake. | *Mothers that received ITN = 94.3<br><br>Mothers that slept under ITN previous night = 70.4%<br><br>Infants that slept under ITN previous night = 79.25% | A pragmatic, cluster-randomized, controlled trial.<br><br>Good sample size and Statistical power 80% Clearly defined inclusion/ exclusion criteria | Confounders were not identified.<br><br>Some data prone to reporting bias. | Availability of essential commodities for the intervention may have affected attrition and coverage. |
| Ameh *et al.* (2016) | "Barriers to and determinants of the use of intermittent preventive treatment of malaria in pregnancy in Cross River State, Nigeria…." | "To identify the barriers to and determinants of the use of SP-IPTp among pregnant women attending ANC in PHC facilities…" | SP-IPTp use | none | SP-IPTp | *SP-IPTp use prevalence = 41% | Define population | Non-RCT cross-sectional questionnaire surveys.<br><br>Prone to reporting bias and Hawthorne effect. | Facility-based study<br><br>Prone to selection bias. |
| Iwuafor *et al.* (2016) | "Malaria Parasitaemia and the use of insecticide-treated nets (INTs) for malaria control amongst under-5 year old children in Calabar, Nigeria" | "To investigate the prevalence of malaria infection and use of insecticide treated nets (ITNs) for malaria control among…" | Malaria testing with RDT and microscopy | none | Mosquito net utilization among the under-fives was low despite high net ownership rate by households | *ITN use = 51.5 %<br><br>*IRS use = 51.1% | Cross-sectional descriptive study design.<br><br>Ethical approval obtained<br><br>Defined population | Not RCT study<br><br>Small sample size<br><br>Questionnaire-based study is prone to reporting bias from self-reported data. | Low external validity due to small sample size and being facility-based |
| Zegers de Beyl *et al.* (2016) | "Multi-country comparison of delivery strategies for mass | "To assess whether the choice of campaign strategy had | ITN campaign | none | proportion of households that received at | Proportion of population within household | Community-household campaign with large | Cross-sectional questionnaire surveys, and prone to | Selection of household was not systematic or random |

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| | campaigns to achieve universal coverage with insecticide-treated nets: what works best?" | any effect on distribution outcomes and whether any other factors can be identified as determinants of successful campaigns" | | | least one ITN from the campaign (also referred to as reach), and the proportion of households with enough nets (defined as having at least one ITN for every two people) | with access to ITN = 44.45% | sample size. | reporting bias and Hawthorne effect. | but opportunistic, hence prone to selection bias. |
| Orobaton *et al.* (2016) | "Scaling-up the use of sulfadoxine-pyrimethamine for the preventive treatment of malaria in pregnancy…" | 1. "Examine scale-up mechanisms that enable increased SP coverage.." . 2. "Examine community acceptance of SP..." 3. "Document associations, if any, between increased SP3 coverage and improved intrauterine conditions for newborn,…" 4. "Estimate the costs of delivering SP at scale per woman for a three doses or higher regimen" | Free IPTp-SP | No free IPTp-SP | IPTp-SP coverage and MCH indices (head circumference and stillbirth) | IPTp-SP3+ coverage = 45% | RCT study design Large sample size, and better external validity. | Prone to measurements bias from head circumference<br><br>Error from misclassification of primary endpoints could result in information bias. | Prone to low Internal validity due to non-stratification of socioeconomic status |
| Koenker *et al.* (2015) | "Impact of a behaviour change intervention on long-lasting insecticidal net care and repair behaviour and net condition…" | "To determine whether behavioural change interventions (BCC) could substantially impact on the average useful life of the net" | LLIN and behavioural change interventions (BCC) messages | none | Access and durability of LLIN | Population having access to LLIN = 39.85% | Cluster cross-sectional household survey RCT (before and after study) | Prone to Effect modification and interaction, and Hawthorn effect<br><br>Low adherence<br><br>No clearly stated aims of study | Limited internal and external validity |
| Onwujekwe *et al.* (2015) | "Effectiveness of provider and community interventions to improve treatment of uncomplicated malaria in Nigeria…." | "To evaluate the effectiveness of the interventions in the context of existing drug supply channels" | RDTs with provider training<br><br>RDTs with provider training plus a school-based community intervention | Rapid Diagnostic Tests (RDTs) with basic instruction | There was no evidence of a difference in uptake of testing due to the interventions. | *39.67%<br><br>(control = 34%; provider arm = 48%; provider-school arm = 37%) | A Cluster Randomized Controlled Trial<br><br>Clearly defined inclusion /exclusion criteria, and outcome measures<br><br>Comparable baseline characteristics | High attrition rate<br><br>Systematic bias due to variation of cluster size.<br><br>Effect modification and interaction due to variation in cluster size<br><br>Possibility of Hawthorn effect | Low internal and external validity due to high attrition rate and variation in cluster size |

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| | | | | | | | Good statistical analysis with sample size powered at 80% | | |
| Wollum *et al.* (2015) | "Benchmarking health system performance across states in Nigeria…" | "To provide the first-ever analysis of state-level trends for a range of Nigeria's key maternal and child health (MCH) outcomes and interventions from 2000 to 2013" | none | none | Nigeria is making notable gains through interventio n. Interventio ns should be more regular to improve coverage | *ITN = 48% *SMC = 29% (IPTp = 20% plus ACTs = 9%) | Systematic review | Prone to statistical or Systematic and interpretation error.<br><br>Few publications included in the review.<br><br>No clearly stated aim of study | Broad scope of review. |

*Coverage is defined as completed treatment or intervention at final endpoint. **Sources of evidence:** BND and ProQuest Central: Okoro *et al.* (2023), Hetzel *et al.* (2023), Falade *et al.* (2023), Balami *et al.* (2021), Noguchi *et al.* (2020), and Onwujekwe *et al.* (2015); BMC Malaria Journal website: Koenker *et al.* (2015), Wollum *et al.* (2015), Iwuafor *et al.* (2016), Zegers de Beyl *et al.* (2016), Ameh *et al.* (2016), and Orobaton *et al.* (2016).

## 3. Findings / Results

The search for evidence was done on ProQuest databases and the BMC website, between 1st and 3rd February 2024, respectively. The combined search identified 2,373 publications that were screened for inclusion eligibility. The abstracts of 26 potentially eligible articles were assessed, and 12 met the inclusion criteria (Figure 1).

Table 2: Summary of data from included evidence

| Interventions category | SMC | ITN or LLIN | IRS | RDT |
|---|---|---|---|---|
| **Reported Coverage (%)** | 33.60 | 22.00 | 51.1 | 39.67 |
| | 52.00 | 94.30 | - | - |
| | 95.90 | 51.50 | - | - |
| | 14.65 | 44.45 | - | - |
| | 41.00 | 39.85 | - | - |
| | 45.00 | 48.00 | - | - |
| | 29.00 | - | - | - |
| **Mean Coverage (%)** | 40.31 | 50.02 | 51.1 | 39.67 |

### *3.1. SMC coverage*

The highest coverage of SMC intervention (95.9%) was that by Falade *et al.* (2023) with an intervention and comparator of Pyronaridine–artesunate and Artemether–lumefantrine, respectively (Table 1). The lowest coverage (14.65%) was by Balami et al (2021) with a health education intervention to promote the uptake of ITN and IPTp. The strength of evidence from the two studies based on hierarchy-of-evidence is strong because they were both randomized controlled trials (RCTs) (Turner, 2014). However, while that of Falade *et al.* was open-label, Balami *et al.* were blinded. Blinded RCTs are less prone to systematic and investigator biases. A major weakness of the RCTs was the small sample size which can limit its external validity. The same challenge was apparent in the evidence by Okoro *et al.* (2023) which reported 33.6% coverage for an intervention involving dihydroartemisinin–piperaquine and sulfadoxine–pyrimethamine, and Orobaton *et al.* (2016) which reported 45% coverage for IPTp-SP intervention. Hetzel et al (2023) studied the effectiveness of pre-referrer rectal artesunate suppositories on child's survival and recorded a coverage of 52%. The large sample size contributed to the strength of evidence but the study design was observational and non-RCT, which contributed to its weakness. A non-RCT study is more prone to biases than RCT studies because it is more dispose to systematic errors and selection bias which cannot be readily adjusted for statistically. The study by Ameh *et al.* (2016) in Cross River State in Nigeria was

questionnaire-based. The authors reported a SP-IPTp use prevalence of 41%. The study was facility-based. The facilities were also not randomized, which made the study prone to selection bias. Wollum *et al.* (2015) systematic review gave a combined coverage of 29% for IPTp (20%) and ACTs (9%) use. Systematic reviews are rated high in hierarchy-of-evidence for evidence-based practice (Turner, 2014).

### *3.2. ITN and LLIN Coverage*

Balami *et al.* (2021) achieved ITN coverage of 22%. The strengths and weaknesses of the evidence were as discussed under SMC coverage. The study has limited external validity because of the small sample size, unclear statistical analysis, and use of a self-reporting questionnaire which is prone to reporting bias. Noguchi *et al.* (2020) compared the effect of group-antenatal care (G-ANC) against standard antenatal care (ANC) in the uptake and use of ITNs (94.3%), in a RCT study design. The design was appropriate but confounding such as socioeconomic status and the effect of health systems were not discussed, contributing to the weakness of the study (LaMorte and Sullivan, 2016). Iwuafor *et al.* (2016) reported a coverage of 51.5% using a non-RCT self-reporting cross-sectional study design. In addition, the sample size was small, limiting its external validity. Non-RCT studies are not rated very high in the hierarchy-of-evidence and self-reporting methods are prone to reporting or information bias (Turner, 2014). Zegers de Beyl *et al.* (2016) also conducted a cross-sectional household-based study with an ITN use of 44.45% using a self-reporting survey questionnaire. However, the validity of the evidence may be impeded by information or reporting and selection bias since the households were not randomly selected. Koenker *et al.* (2015) behavioural change campaign achieved a coverage of 39.85% long-lasting insecticide nets (LLINs) usage. The study used a repeated cross-sectional household survey and before and after study design, which is prone to Hawthrone effect (McCambridge *et al.*, 2014). Wollum *et al.* (2015) also reported 48% ITN use. The strength and weakness of the evidence have been discussed in the preceding SMC section.

### *3.3. IRS and RDT Coverage*

Onwujekwe *et al.* (2015) studied the "effectiveness of provider and community interventions to improve treatment of uncomplicated malaria" with RDTs using a cluster-RCT study design. The intervention attained a coverage of 39.67%. Though the strength of evidence appears strong due to the RCT study design, it was however prone to statistical bias due to variation in cluster sizes. Iwuafor *et al.* (2016) reported IRS coverage of 51.1%. The strengths and weaknesses of the study discussed in the preceding ITN section also applies.

## 4. Discussion

The evidence from this review showed that the average intervention coverage for SMC, ITNs/LLINs, IRS and RDT interventions, were 40.31%, 50.02%, 51.1% and 39.67% of targeted population, respectively. The review indicates that recent peer-reviewed publications on malaria intervention coverage in Nigeria are few. More so, it included only one systematic review by Wollum *et al.* (2015), and seven RCTs viz; Balami *et al.*, (2021), Falade *et al.* (2023), Koenker *et al.* (2015), Noguchi *et al.* (2020), Okoro *et al.* (2023) and Orobaton *et al.* (2016). Only the RCTs by Orobaton *et al.* could be considered to have had an adequate sample size to strengthen external validity. However, its internal validity was in question due to the non-stratification of the participants' socioeconomic status. The sample sizes of the other RCTs raised questions about the external validity of the studies.

The implication of the seemingly persistent low level of coverage is far-reaching on the malaria eradication and elimination targets by WHO and NMEP, respectively. It is estimated that over 97% of Nigerians are at risk of malaria population (PMI, 2022). With an average intervention coverage of about 50.56% (mean of ITN and IRS) for vector control, and 40% (SMC and RDTs) for diagnosis and treatment, there exists a huge gap to be met. Of all the SMC interventions, only 28.6% (2) attained a coverage of over 50%, and only 14.3% (1) had a coverage of 95% but with a limitation of small sample size. A similar challenging profile could be seen for the vector control interventions (Tables 1 and 2). The upward trajectory of malaria elimination interventions is a slow-gradient slope, and much progress seemed not to have been achieved over the last 9 years. The SMC during antenatal in 2015 was 37% (Noguchi *et al.*, 2020), and this is not significantly different from the average of 40% reported for the 9 years

after with only 3% marginal increase in coverage. This amounts to about 0.33% change annually or a 2% in the next 6 years going by the current momentum. This will translate to an average coverage of about 42.% by 2030. To meet the target set by NMEP (80%) and SDG, a minimum annual incremental coverage of about 6.3% is needed. This means multiplying the current effort by about 20 folds. A similar trajectory is estimated for the other intervention components. The implication of this is that the country needs to review its framework of intervention and mobilize adequate resources if it is to make reasonable progress toward the set targets.

The challenge of intervention coverage has been identified as multifaceted by many authors (Noguchi *et al.*, 2020). The enrolment and attrition of participants from interventions could be traced to many factors related to inequities, inequalities, and operational and logistics gaps including the availability of commodities, as well as knowledge and proficiency of health workers and caregivers. For instance, multidimensional poverty makes it difficult for some participants to adhere to treatment or programme regimens since time spent on participation may translate to lost man-hours and revenue. Gender-related inequality in health behaviours and cultural beliefs and practices, for instance, the nomadic culture, also play roles in treatment access and adherence (Haileselassi *et al.*, 2023; Ricci, 2012). Another growing challenge is the rising number of internally displaced persons who live in suboptimal vector-prone shelters due to political instability, insecurity from terrorism, natural disasters and environmental pollution (Solanke *et al.*, 2023). A contextual framework that could promote health-seeking behaviours and hygiene, reduce the level and impact of poverty and internal displacement, and increase knowledge and awareness to correct misleading harmful or health-hindering cultural practices could help improve and sustain adherence to programme and intervention coverage (Ibinaiye *et al.*, 2024; Solanke *et al.*, 2023). Such a framework needs proper planning and adequate resource mobilsation for year-round and multiyear intervention.

### *4.1. Limitation of study*

This study was limited by the small number of articles that met the inclusion criteria. Hence, a meta-analysis could not be undertaken. Only one article each was available for IRS and RDT, and their "mean coverage" was not a statistical calculation. Hence, this may be a source of interpretation bias (Gutbezahl, 2021). In addition, the computed means may not be a true representation of the current trends which ought to be computed on an annual basis but for the inadequate publications. It is recommended that more peer-reviewed studies on coverage and the matrix of all intrinsic and extrinsic factors interloping between intervention coverage, vector control, and parasite prevalence be conducted to establish the true trend to adequately project and estimate the feasible date for meeting the SDG target 3.3.3. Furthermore, the review was undertaken by two authors only which makes it prone to selection, reporting, and interpretation bias, as some studies that were excluded could have been included from the perspective of a third or fourth reviewing author, and vice-versa.

## 5. Conclusion

The SDG goal that is focused directly on promoting healthcare is Goal 3, 'ensuring healthy lives and well-being for everyone through all ages'. Attaining this goal, depends on the attainment of a number of targets to address global burden of diseases. For instance, target 3 is focused on addressing infectious diseases including malaria, TB, and HIV/AIDs which greatly affect low- and medium-income countries like Nigeria. Nigeria is the leading contributor to the global burden of malaria. Malaria is largely responsible for Nigeria's poor health and socioeconomic indices resulting in huge economic losses annually. The fight against malaria in the country is led by the Federal Ministry of Health through NMEP. The parasite prevalence and mortality target set by the NMEP for 2025 is <10%, and <50 deaths per 1,000 live births, respectively. The intervention commodities coverage targets include ≥80% utilization of vector control interventions (ITNs/LLINs and IRS), and ≥80% access to chemopreventives and diagnostics for appropriate treatment. Recent evidence indicates that the trend in malaria prevalence in Nigeria is a very slow decline if at all there is any decline despite several interventions by government and development partners (Omojuyigbe *et al.*, 2023). This challenge has been hinged on un-sustained programmes and limited coverage determined by several factors. The attainment of target 3.3.3 of the SDG and the vision of NMEP to eliminate malaria from Nigeria is dependent on achieving ≥80% coverage for vector control and parasite elimination interventions. This systematic review considered available evidence in the literature to answer the research question "is there any evidence that the current level of malaria intervention coverage can

help reduce malaria case incidence and mortality by 90% each in Nigeria by the year 2030". Of the 2,373 articles systematically searched on ProQuest databases and BMC Malaria journal website (Figure 1), only few peer-reviewed publications (twelve) met the inclusion criteria for the review, and the quality of each evidence (validity and reliability) was assessed and discussed using the CASP assessment tool. The review indicated that the average coverage of malaria intervention remained low over the past nine years at about 40.31%, 50.02%, 51.1% and 39.67% for SMCs, ITNs/LLINs, IRS and RDTs, respectively. Improving the coverage of interventions to ≥80%, and sustaining it is imperative to achieving malaria elimination targets and SDG 3 for Nigeria, specifically, SDG targets 3.3.3 and the NMEP target 0:10:5:80:80. A multiyear context-specific multiplicity of effort should be adopted and sustained over the next 6 years to meet the targets. Resolving the challenge of improved coverage is mediated by many factors including funding, commodities logistics, culture and lifestyle, and socioeconomic status of the targeted population, etc. The strategy and framework for improving malaria intervention coverage have to be multisectoral to address multidimensional poverty, hygiene, wrong perspectives, health-hindering cultural practices, and limited knowledge about the disease in the targeted population (Ibinaiye *et al.*, 2024).

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# A Comparison of Healthcare Funding Systems between Low-/Medium-Income and High-Income Countries: Equity, Equality, and Fairness in the Rationing of Healthcare Resources

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**Abstract**
Access to healthcare is a social right and its demand is universal. However, health resources are limited and have to be rationed justifiably which borders on societal values and the efficiency of the healthcare system. A more efficient health system will promote more equitable access to health care based on the principle of universal health coverage (UHC) advocated by the World Health Organisation. The efficiency of any health system depends on the structure of its funding or financing system. Evidence has shown that there is a strong correlation between country's income and total health expenditure. This also affects the health financing systems of countries. This discourse exposes the challenge of health inequities/inequalities and its correlation with health funding systems in low-income countries and upper-middle/high-income countries using Nigeria and the United States as reference countries. It also attempts to discuss the feasibility of attaining more equitable access to healthcare in a manner that promotes health equity and equality through economic evaluations of interventions in diseases of high socioeconomic burden and major health outcome concerns.

**Keywords:** Health Funding Systems, Healthcare, Inequities, Inequalities, Rationing, Cost-Effectiveness Analysis, Malaria, Cardiovascular Disease, Nigeria, United States

## 1. Introduction

Governments all over the world exist for the social good of the people and seek to improve the health status of their citizens. Improving the health status directly improved health outcomes such as disease morbidity and mortality, as well as quality of life. Better health outcomes are achieved through better health systems, and quality of living which may not be dependent on healthcare delivery alone but also on other social, economic, and environmental factors (Ejughemre *et al.*, 2015; World Health Organisation, 2006, p. 5). Thus, the structural framework for sustainable governance of a good health system is enormous, crosscutting, and intricate. It requires the development of human resources, the harnessing of financial resources, and the development or acquisition of appropriate infrastructure and technology for quality service delivery (World Health Organisation, 2006, p. 5).

Improving the quality of healthcare of the population is influenced by the level of access to healthcare services which is determined by access to qualified personnel, quality medications, appropriate technologies, nearby facilities, and alternative care. All these determinant factors are moderated by costs and health information and therefore can be affected by the income, educational status, and neighbourhood of the care recipient. Income and educational status are key indices that affect the socioeconomic status of individuals in a community, which in turn determine the social strata to which an individual belongs. Social strata of society affect the level of access to public facilities and amenities and raise the question of equity and equality (Donaldson and Rutter, 2018, p. 153-168).

Health as a basic need and a social right poses the challenge of equity and efficiency in the allocation of health resources, and raises the question of appropriate governance structure and the role of government in health systems. A good health system will promote good health outcomes, equity and sustenance of societal or cultural values (World Health Organisation, 2006, p. 5). As the custodian of inherent resources (natural and tax resources), and policies, government plays major roles in health systems development including planning, financing, and management, through appropriate mobilisation and equitable distribution of resources. The most critical of this is health system financing, which modulates the healthcare funding system and structure. Financial resources are the most cut-crossing and relevant to developing and acquiring other resources. However, like other resources, it is limited and presents healthcare with the challenges of rationing, equity, and efficiency (Scheunemann and White, 2011).

### *1.1 Worsening Inequality/Inequity and Sustainable Health Financing*

Rationing is the allocation of scarce resources based on perceived priority and/or overall benefits, which in health care inevitably requires withholding potentially beneficial treatments from some individuals. Fundamental to the discussion of rationing is whether the potential benefit is large enough or likely to occur to justify the expense. Thus, it borders on the consideration of societal values and the efficiency of the healthcare system. It is important to note that not all efforts to control healthcare costs involve rationing. Rationing requires the principles of distributive justice or equity, viz: "to each person an equal share," "to each according to need," "to each according to effort," "to each according to free market conditions," and "to each so as to maximize overall usefulness" (Scheunemann and White, 2011). In rationing, there is always a competing scenario between efficiency, equity (and equality), and "rue of rescue" or the innate human desire to save life or help alleviate the situation.

The current global inclination towards democracy and capitalism presents greater reliance on market forces for resource allocation. Thus, health systems across the world are financed through a mix of funding schemes from corporate and individual resources, which do not promote equity, equality, and fairness in the societal essence. The Corporate financial resources come from the government, private sector, and donors (international development partner organisations, and charitable non-governmental organisations), while individual resources come from personal out-of-pocket spending (OOPS) (McIntyre, 2007; World Health Organisation, 2006, p. 5).

Studies have shown globally that, there is a positive correlation between per capita income and/or gross domestic product (GDP) per capita, and total health expenditure. An analysis of national health accounts has shown that government spending, as a percentage of total health expenditure, has decreased over time in most middle- and low-income countries. This has raised the burden of healthcare costs on households and communities and has further worsened poverty and widened inequity (McIntyre, 2007; Umukoro, 2012; World Health Organisation, 2005).

In a bid to mitigate the worsening inequalities (and inequities) in access to health and promote Universal Health Coverage (UHC), the fifty-eight World Health Assembly (WHA 58.33) on sustainable health financing, universal coverage, and social health insurance, recommended the development of a health financing system in member countries that ensure access to essential health services and financial-risk protection through prepayment and pooling of resources (World Health Organisation, 2005). Thus, the financing mechanism advocated is one that can protect individuals from "catastrophic healthcare expenditure and impoverishment" as a result of accessing healthcare. The resolution also extends to the equitable distribution of good-quality healthcare infrastructures and

human resources to allow for equitable and fair access to quality care, within the macroeconomic, sociocultural, and political context of countries. The UHC is the focus of Sustainable Development Goal 3, Target 8 (SDG 3:8); and plays relevant roles in poverty reduction (SDG 1), gender equality (SDG 5), inclusive economic development (SDG 8), and reduction in general inequalities (SDG 10) (Adelakun, 2022). Contemporary approach to sustainable healthcare funding advocates progressive pool funding, risk-sharing and/or subsidy, and promotes the principle of ethical rationing involving equity, equality, and fairness in accordance with the principles of UHC (Adelakun, 2022; Ejughemre *et al.*, 2015; Raine *et al.*, 2016).

The ethical problem of inequity and inequalities is more pronounced in low- and medium-income countries and continues to challenge the attainment of UHC. This paper discusses the health financing systems of Nigeria and the United States of America as examples of low/medium-income and high-income countries, respectively. It attempts to describe the distribution of costs and benefits structure of programmes targeted at key healthcare outcomes of concerns, and the allocation of health resources within the context of equity, equality, and fairness.

## 2. Discussion

### *2.1. Health Funding System in Nigeria*

A recent World Bank report indicates that 40% of Nigerians live below the national poverty line of about US$1.93 per person per day, with many lacking education and access to basic infrastructure (electricity, safe drinking water, and good sanitation). The rural communities are worse off with about 52.1% poverty rate. Huge out-of-pocket expenditures are made on health and education, as well as an array of other non-food items such as transport, fuel, electricity, household items, and clothing (The World Bank, 2022a, p. 11-14)

The current World Health Organisation (WHO) national health account data on financing schemes as a percentage of current health expenditure (CHE) for the year 2020 estimates that in Nigeria, OOPS accounts for approximately 75%, while government schemes and compulsory contributory (social) health insurance schemes account for about 15% and 1%, respectively (WHO, 2023; The World Bank, 2023). This structure of healthcare financing which relies heavily on OOPS has not only proven to be unprogressive, and financially unprotective of the poor but also promotes inequality and catastrophic health spending, as well as impoverishment of the vulnerable group and the poor who live below US$2 a day (Adekunle, 2022; Ayogu *et al.*, 2021; Olakunde, 2012; Oyibo, 2011). Fortunately, the recently signed National Health Insurance Authority Act (2022) gives a ray of hope to the poor and vulnerable. The National Health Insurance Authority (NHIA) Act made provisions for the vulnerable poor through the institution of the Basic Health Care Provision Fund (BHCPF) and Vulnerable Group Fund (VGF) for free healthcare coverage. The Act provides for mandatory health insurance for all residents, and incorporates mechanisms for the subnational (State) level actors to access the Funds. It promises to promote the fundamentals of UHC if properly implemented (National Health Insurance Authority, 2022).

#### 2.1.1. Malaria Morbidity and Mortality as Major Health Outcomes of Concern in Nigeria

Since 2010, malaria, HIV/AIDS, and lower respiratory infections have been the leading cause of disability-adjusted life years (DALYs), low quality of life, and unexpected deaths in Nigeria (Murray *et al.*, 2020; Institute for Health Metrics and Evaluation, 2023). A recent study indicates that malaria and neo-natal disorder are the leading causes of years of life lost (YLLs) by Nigerians (Angell *et al.*, 2022). The country accounts for 31.3% of global malaria deaths and also leads with 38.4% of malaria deaths in under-5 children (WHO, 2022, p. 17). Malaria has long been associated with poverty and is predominantly transmitted in poor neighbourhoods. It is responsible for catastrophic personal healthcare spending, and loss of income as a result of absence from work. A large portion of the OOPS segment of the total health expenditure of Nigeria is due to malaria (Ayogu *et al.*, 2021). Thus, reducing the malaria epidemic in the country will contribute greatly to the principles of UHC and the attainment of the already outlined SDGs (Adelakun, 2022).

Several interventions have been targeted at eradicating the disease in some communities and geo-locations in Nigeria with minimal success due to the unabating high transmission rate, poverty, and entrenched inequalities.

In cost-effectiveness analysis of malaria programmes such as vector control (through larvae source management (LSM) or insecticide-treated nets (ITNs) or long-lasting insecticide nets (LLINs)), seasonal malaria chemoprevention (SMC), and treatment with artemisinin-based combination therapies (ACTs), the distribution of costs cut across; (i) non-recurrent or indirect costs (capital cost such as building, machineries for specialized technologies or services for opportunistic ailments or co-morbidities), personnel (field, hospital consultation, laboratory analysis, and data); (ii) direct cost of intervention key items (i.e., nets, insecticides, machinery, and drugs), stationaries, supplies, information/education/communication (IEC), storage, training, distribution, administration, registration, data collection and analysis, telephone, transport, management, supervision, monitoring, hospitalization, non-specific costs (family caregiver and lost income, etc.), and (iii) utility-based cost such as unexpected deaths, related deaths, etc. (Avanceña *et al.,* 2022; Centre for the Study of the Economies of Africa, 2012; Conteh *et al.*, 2021). Effectiveness (benefits) have been assessed based on, (i) field activities or non-clinical outcomes such as doses administered, rounds of treatments (or doses) per year or season, nets distributed, cases tested, cases diagnosed (presumptively, rapid diagnostic test (RDT), microscopy), cases treated (complicated, severe, uncomplicated), degree of coverage, and retention in care or follow-up; (ii) clinical outcomes such as a reduction in transmission rate, parasitemia, new infections, and adverse events and serious adverse events (AE/SAE); and (iii) utility outcomes such as quality-adjusted life years (QALYs) gained, life years (LY) saved, healthy life years (HLYs), DALYs averted, number of persons protected, infant deaths averted, Children under-5 protected, clinical cases or episode averted, etc. (Avanceña *et al.,* 2022; Ayogu *et al.,*2021; Conteh *et al.*, 2021; Gunda, and Chimbari, 2017).

Ezenduka *et al.* (2017) estimate that treatment of uncomplicated malaria consumes about 25% of the annual budget of public health facilities in Nigeria at the cost of over US$31 per case, with personnel cost accounting for approximately 83% of the costs. An earlier study by Onwujekwe *et al.* (2013, as cited in Ezenduka *et al.*, 2017, p. 186) estimates between US$30.42 and US$48.02 as recurrent provider cost per case of malaria treatment for each outpatient and inpatient care, respectively, while US$133.07 and US$1857.15 were the non-recurrent provider costs per case, respectively. An analysis of the direct cost for treatment of uncomplicated malaria by Ayogu *et al.* (2021), indicates that the mean cost of antimalarial drugs (using artemisinin-based combination therapies [ACTs]) per treatment episode was $1.96, which is higher than the specified poverty line of US$1.93. The cost outlay from reported studies suggests that the cost of treatment of a single episode is above the Nigerian poverty line, thus, making treatment unaffordable for poor and vulnerable groups i.e., children, adolescent girls, women, the elderly, malnourished people, and those who are ill or with pre-existing health conditions or disabilities, as defined in the National Health Act (2014). The study by Conteh *et al.*, (2021) also substantiates this position.

Given the cost-benefits outlay of malaria treatment, a method of distributing costs and benefits will have to consider the vulnerable groups in order to adapt programmes towards more equitable healthcare access. For instance, the inclusion of the BMPC and VGF in the NHIA Act, which is a step in the right direction. The VGF allows the vulnerable to access health insurance for free without paying the required enrollees' premium, co-payment of 10% for drugs, and co-insurance for specialized treatment of laboratory investigations covered under the partial exclusion list (National Health Insurance Scheme, 2012, p. 17). However other economic and financial incentive programmes such as conditional cash transfer, transport reimbursement, and hospital meals may help to bridge the widening gap in equity and equality since this will promote accessibility and affordability among the vulnerable. Although the distribution of public health facilities may be considered fairly equitable, the same cannot be said about private facilities which are concentrated in the urban centers. Likewise, the distribution of qualified personnel is inequitably skewed toward the urban settlements (Adegoke *et al.*, 2017; Azodoh and Obitube, 2022; Kum, 2020, p. 27-34; Uneke *et al.*, 2007). A 2021 data from The World Bank (2022b) shows that about 47.25 % (100,840,661) of Nigerians live in rural areas, which also house the majority of the poor. Hence, there is a need to provide more facilities and personnel for more equitable access to healthcare.

### *2.2. Health Financing System in the United States of America*

In contrast to the financing structure in the Nigerian health system, the WHO national health account data for the United States of America (USA) indicate the structure of health funding as OOPS (10%), government schemes

(33%), compulsory (social) health insurance schemes (22%), compulsory private insurance schemes (29%), and the balance is spread between voluntary health insurance scheme (1%), and non-profit institutions serving households financing schemes (4%) (WHO, 2023). According to the 2019 data from the Pan American Health Organisation (2021), the leading causes of death and disabilities in the USA are cardiovascular disease (CVD), where Ischaemic heart disease (15.2%), and stroke (6.7%) are major contributors. Other contributors to CVD include circulatory diseases, hypertensive heart disease, cardiomyopathy, myocarditis, endocarditis and rheumatic heart disease. This is unlike the low-/medium-income countries in sub-Saharan Africa where infectious diseases, such as malaria and HIV/AIDS, are the leading causes of death.

2.2.1. Cardiovascular Disease (CVD) Morbidity and Mortality as a Major Health Outcome of Concern in the US

According to the Centers for Disease Control and Prevention (CDC), about 805,000 people have heart attacks each year, and CVD was responsible for 695,000 deaths (about 20%) in 2021 (CDC, 2023a). The disease correlates with certain lifestyle behaviours. Some interventions targeted at risk reduction through lifestyle changes such as promoting smoking cessation, physical activity, and quality diets, have shown conditional effectiveness (Smith *et al.*, 2019). The cost-effectiveness analysis of CVD interventions has shown cost outlays covering the cost of programme personnel, cost of serious adverse events (stroke, acute myocardial infarction, surgery), and other direct costs (laboratory diagnostic tests, drugs, hospitalization, follow-up, point-of-service cholesterol/diabetes screenings, physical activity programme, tobacco control programme, etc). Although output and outcome targets may include lower blood cholesterol, lower blood pressure, and blood sugar, the benefits in cost-effectiveness analysis (CEA) are usually assessed using utility indices such as QALYs gained, and DALYs averted (McCreanor *et al.*, 2018; Smith *et al.*, 2019). Since clinical effectiveness and cost-effectiveness are considered important in determining insurance coverage in the USA, the use of utility indices which makes CVD programmes cost-effective in the long run confers a necessary advantage to the care receiver. Fortunately, However, the use of CEA (CUA) in policy and decision-making remains a contentious issue. (Eze-Nliam *et al.*, 2015).

Like Nigeria, and though in a different context and framework, health inequity has remained a persistent challenge in the US (CDC, 2023b). Some racial and ethnic minority groups are discriminated against in terms of access to health compared to their white counterpart. People living with disabilities and people from some racial and ethnic minority groups, rural areas, and white populations with lower incomes are more likely to face multiple barriers to accessing healthcare (CDC, 2023b). The CDC has tried the mitigate the problem of inequities through programmes like “Health Equity in Action” which uses best practices to spotlight projects that align with CDC’s CORE (Cultivate, Optimize, Reinforce, Enhance) commitment and shares the lived experiences of communities advancing health equity. With respect to CVD, regular checks for CVD risk factors, and focused lifestyle change programmes among vulnerable groups such as poor neighbourhood could promote equity. A recent review by Cheng *et al.* (2023) suggests that ensuring food security and diet quality could close CVD morbidity and mortality gaps among socioeconomic strata and prioritizing such interventions among high-risk groups in a multi-level approach could reduce inequity.

## 3. Implication

In consideration of sustainable health care financing and UHC, health inequity (and inequalities) based on race, ethnicity, and socioeconomic disparities, especially due to education, income, and neighbourhood, is a global challenge, which needs to be addressed in the true essence of distributive justice due to unavoidable rationing of limited resources (Scheunemann and White, 2011). Existing healthcare financing in Nigeria, which is highly dependent on OOPS with consequent huge economic burden, catastrophic spending, and impoverishment of the poor and vulnerable groups is regressive and unsustainable. Such a financing system is inimical to the principle of UHC, unlike the US where OOPS is relatively low and there is a fair mix of the financing structure among different schemes (WHO, 2023).

Over 90% of the Nigerian population is at risk of malaria, and associated OOPS is mainly spent on consultation, drugs, laboratory diagnostic tests, and transport. Vulnerable groups are unable to afford these costs and acquire preventive ITNs (LLINs). Moderating equity (and equality) of service requires careful consideration of

programmes and the targeted population (Raine *et al.*, 2016). Programmes of vector control targeted at poor neighbourhoods are appropriate since they promote equity (and equality) of access to ITNs (LLINs), and a better environment through larvae source management (LSM). The seasonal malaria chemoprevention (SMC) programme with ACTs also has the potential of promoting equity in malaria prevention and treatment if properly implemented. For the treatment of clinical cases, the NHIA Act has provided for the BHCPF and VGF for free healthcare service. The envisaged challenge with the Funds will be the availability of a reliable national social registry of the poor and vulnerable from the National Social Safety Nets Coordination Office (NASSCO) of the National Social Investment Programme (NSIP), the advocacy and effective engagement of stakeholders, and coordination of the HIS by NHIA. Since not everyone is captured under the vulnerable group, the sustainable financing of malaria healthcare services will require the progressive pooling of funds and efficient insurance schemes.

Likewise, ration within cardiovascular disease healthcare service in the US is a matter of between surgery (including hospitalization) and the various lifestyle change programmes. The challenge of inequities (and inequalities) that creates discrimination among minority groups and certain races by care providers could be addressed by the provision of adequate facilities, stricter monitoring of standards in poor neighborhoods, and the institution of a more transparent system of reporting the quality of service by care receivers. Perhaps the major challenge that may be confronting the US government is how to maintain or further reduce the OOPS from the current 10% to possibly less than 5% so that a sizeable proportion of its population is not subjected to catastrophic health spending (Jalali *et al.*, 2021).

## 4. Conclusion

Resources are limited but needs are not. This imbalance creates the need for rationing of resources based on priorities. The concept of rationing requires the principle of distributive justice and equity. Disparities in the socioeconomic status of individuals or groups in the population result in health inequalities and inequity. Attempts at addressing health inequities led to the adoption of the concept of sustainable health financing through health insurance, and the proclamation of UHC by the WHO (WHO, 2005). The structure of health funding systems across the world varies from country to country with similarities within national income brackets. The structure is a mix of financial resources from corporate (government, private, and donor organisations) and individual resources (OOPS) (McIntyre, 2007; World Health Organisation, 2006, p. 5). While health funding systems are well distributed across pool-funding and insurance schemes with minimal OOPS in high-income countries like the US, the system is poorly distributed in low-/medium-income countries like Nigeria, where it is highly skewed towards OOPS resulting in catastrophic spending. This places a huge economic burden on the poor and vulnerable in the lower socioeconomic stratum, which negates the principles of UHC.

Achieving equity in the rationing of resources for malaria treatment and elimination in Nigeria requires careful consideration of strategy for reducing OOPS especially among the vulnerable groups. The provisions of the NHIA Act (2022) will appropriately respond this OOPS by vulnerable groups if properly implemented. A well-planned vector control and SMC programmes targeted at more vulnerable neighbourhoods and populations could also provide palliative measures for equity. The US could promote equity in CVD healthcare by improving health insurance coverage and focusing lifestyle change programmes on poor neighbourhood and vulnerable groups.

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# Serum Vitamin D Level and Insulin Resistance in Obese Adolescent with Polycystic Ovary Syndrome (PCOS)

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**Abstract**

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility, and biochemical and clinical hyperandrogenism. The objective of this study was to evaluate the serum vitamin D Level and Insulin Resistance in Obese Adolescents with polycystic ovary syndrome (PCOS). The study was a cross-sectional study conducted among 94 PCOS women of reproductive age coming to the Department of Endocrinology & Metabolism of Bangabandhu Sheikh Mujib Medical University (BSMMU). The women with polycystic ovary syndrome were considered as the study population. Among the participants, around 91% had vitamin D deficiency and 4% had vitamin D insufficiency, no participants had a sufficiency. Among PCOS patients underweight was 42.10%, Healthy Weight 45.27%, pre-obese 9.63%, and obese 3.0%. Regarding fasting insulin levels (<20uIU/ml) among 14.9% of PCOS. In the comparison of clinical characteristics of the participants, less than half (37.2%) had painful menstruation and 67% had hirsutism. Adolescent girls with PCOS are mostly vitamin D deficient and the rate of obesity is also high. The results of this study brought the true picture of insulin resistance and metabolic syndrome among different phenotypes of women with PCOS in Bangladesh, very likely contributing to a better understanding of the management of PCOS, and patients will benefit individually in their

management. Estimation of vitamin D levels & and examination the obesity may help the clinician to manage obesity cases with PCOS adolescents more efficiently.

**Keywords:** PCOS, Serum Vitamin D Level, Insulin Resistance, Metabolic Syndrome, Adolescent girls

## 1. Background

Polycystic ovary syndrome (PCOS) is a complex disorder affecting the hypothalamic-pituitary- ovarian axis with an estimated prevalence of 5-10% in reproductive age women (Ehrmann, 2005). PCOS is characterized by chronic anovulation leading to menstrual irregularities and hyperandrogenism associated with hirsutism and acne. PCOS is often associated with obesity andinsulin resistance leading to metabolic disturbances including impaired glucose tolerance, type 2 diabetes mellitus, and dyslipidemia (Wild et al., 2011). Other associated health concerns include infertility, endometrial hyperplasia, and cancer. Vitamin D is thought to regulate gene transcription through vitamin D receptors (VDR) that are widely distributed in tissues including ovaries (Ehrmann, 2005). Lower, similar, and higher concentrations have been reported in women with PCOS (Thys-Jacobset al., 1999; Rashidi et al., 2009; Parikh et al., 2010). Given the high rate of obesity among womenwith PCOS and the fact that, in the general population, a low concentration of vitamin D has beenassociated with obesity (Pal et al., 2012; Raja-Khan et al., 2014). Elevated androgen levels in PCOS cause unfavorable derangements in adipose tissue and in glucose metabolism (Tsakova et al., 2012). It has been proposed that the connection between vitamin D and PCOS arises from theendocrine pathways affected in PCOS, such as sex hormone synthesis and insulin secretion (Yildizhan et al., 2009; Mahmoudi et al., 2010). However, clinical trials involving vitamin D supplementation in women with PCOS have shown conflicting or weak results in terms of improving insulin sensitivity and other metabolic factors, such as low-grade inflammation and androgen levels (Gordon, et al., 2004; Dong et al., 2010; Holick et al., 2011). Vitamin D has important roles in various parts of the body, especially in the bones. The active form of vitamin D plays an important role in bone metabolism, regulation of calcium-phosphorusequilibrium, and cell differentiation and proliferation (Walter 1992, Studzinski et al., 1993). Vitamin D deficiency is quite common in the general population. In fact, in several studies, vitaminD levels were found to be below 20ng/mlin10-60% of adults (Prentice 2008, Lips 2010). Serum 25-hydroxy vitamin D (25-OHD) concentrations of below 20ng/ml are considered as vitamin D deficiency and serum 25-OHD concentrations of 20-30ng/ml are considered as vitamin D insufficiency (Holick 2007). 1.25-OHD increases insulin synthesis and secretion (Teegarden et al.,2009) and regulates steroid oogenesis in the human ovarian tissue (Parikh et al., 2010). In addition, genetic PCOS related to vitamin D receptor variances has been described (Ranjzad et al.,2011).

In the light of this information, there is a debate about whether vitamin D deficiency plays a role in PCOS pathogenesis. Studies comparing vitamin D levels between patients with PCOS and healthy adolescents with normal ovulation have yielded conflicting results. Some studies have shown that vitamin D levels do not change in patients with PCOS (Li et al., 2011, Panidis et al., 2005), while others have reported higher levels (Mahmoudi et al., 2012)or low levels (Wehr et al., 2010, Mazloomi et al., 2012) of vitamin D. A study by Begum F, 2009 showed insulin resistance was 42% in PCOS patients and another studyby Islam S, 2015 showed metabolic syndrome in PCOS patients was 15.3% in Bangladesh. To ourknowledge, no study has yet been done to see the vitamin D status of PCOS adolescent patients inBangladesh. So, the present study is designed to determine the status of vitamin D in PCOS adolescents and to find out its relationship with BMI in polycystic ovary syndrome in Bangladesh.

This study focuses on the serum vitamin D level and insulin resistance in obese adolescents with polycystic ovary syndrome (PCOS).

## 2. Methodology

This cross-sectional study was conducted in the Department of Endocrinology & Metabolism of Bangabandhu Sheikh Mujib Medical University (BSMMU) for a year period. The adolescent with polycystic ovary syndrome (PCOS) was considered as the study population. In this study totalof 94 adolescent girls with PCOS were enrolled

who visited the Endocrinology and Metabolism Department for treatment purposes. Written informed consent was taken from their guardians andverbal consent was taken from the participants. PCOS was diagnosed by Rotterdam criteria. Theparticipants were unmarried adolescents aged between 17-19 years. A semi-structuredquestionnaire was used to collect the data by face-to-face interview. To estimate the Vitamin D level blood sample were collected between 8 am to 10 a.m. Then vitamin D levels were estimated.The [25(OH) D] cutoffs to define deficiency and insufficiency vary and have most recently been framed by the 2011 desirable levels of the Institute of Medicine Report and the Endocrine SocietyGuidelines. According to these guidelines, vitamin D deficiency was defined in the present studyas a concentration of 25(OH) D < 20 ng/mL and between 20 and 29.9 ng/mL as insufficiency and a concentration ≥ 30/mL as sufficient. The BMI of the participants was calculated using a standard formula, BMI=Weight (kg) / [height (m)]$^2$ and classified according to the WHO guideline (WHO,2021)

## 3. Results

Table 1 shows the socio-demographic parameters of the participating adolescent girls. Most of theparticipant's (48.2%) age was ≥ 16 years. 87% of the respondents were unmarried and around 48.9% of the participants had family member's ≥5. Around 29.8% of the parents of the participantswere private service holders. Around half of the participants (48.9%) had less than 40,000 takas monthly family income. Next to them, 39.4% of the participants had a family income of 40000 to1 lac taka.

Table 1: Sociodemographic characteristics of the respondents (N=94)

| **Characteristics** | | ***n* (%)** |
|---|---|---|
| Age (years) | < 16 years | 46 (46.5) |
| | ≥ 16 years | 48 (48.5) |
| Marital status | Married | 8 (8.1) |
| | Unmarried | 86 (86.9) |
| Family Member | <5 persons | 48 (51.1) |
| | ≥5 persons | 46 (48.9) |
| Parents Occupation | Government Service | 7 (7.4) |
| | Private Service | 23 (24.5) |
| | Businessman | 13 (13.9) |
| | Farmer | 28 (29.8) |
| | Labor | 23 (24.5) |
| Monthly Family Income | <40000 | 46 (48.9) |
| | 40000-1 Lac | 37 (39.4) |
| | >1 Lac | 11 (11.7) |
| Monthly Family Income (In thousand) [Mean±SD] | | 51968±33725 |

Figure 1 shows the vitamin D level of the respondents. The mean Vitamin D of the patients was 13.13±3.27 ng/ml. The majority of the participants, 90.9% had deficient vitamin D levels as < 20 ng/ml. Only 4% of participants were in the insufficient level of vitamin D as 20-29.9 ng/ml. In this study, no respondents had a sufficient level of vitamin D as ≥ 30 ng/ml.

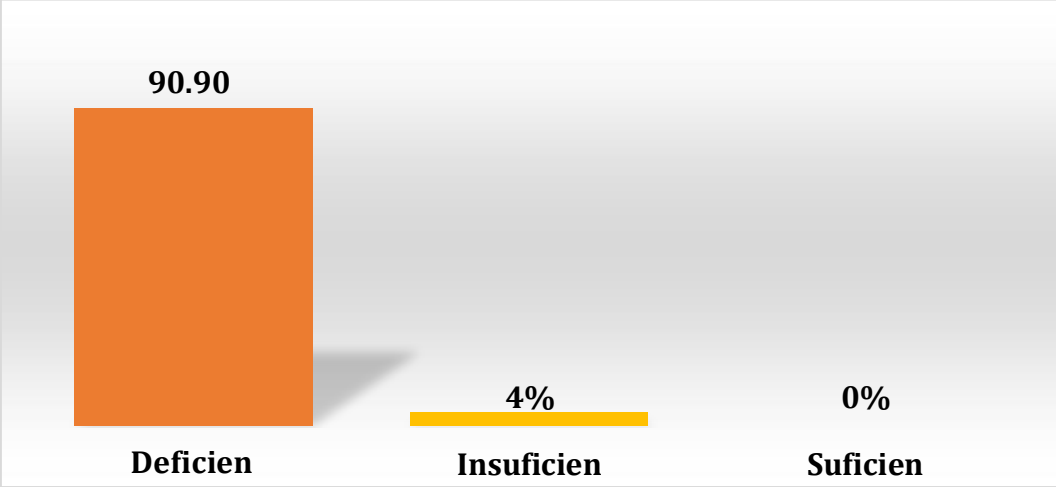


Figure 1: Vitamin D level of the respondents

Table 2 shows the clinical characteristics of the participants. Here participants with irregular menstruation were 100%, lower abdominal pain 37.2%, hirsutism 67.0%.

Table 2: Clinical characteristics of respondents

| **Characteristics** | | ***n* (94)** | **%** |
|---|---|---|---|
| Menstruation cycle | Irregular | 94 (100) | |
| Lower Abdominal Pain | Yes | 35 (37.2) | |
| | No | 59 (62.8) | |
| Hirsutism | Yes | 63 (67.0) | |
| | No | 31 (33.0) | |

Figure 2 shows that 47.5% of respondents were underweight, 34.3% within the normal range. Around 10.1% of respondents were pre-obesity and only 3% of respondents were in Obesity.

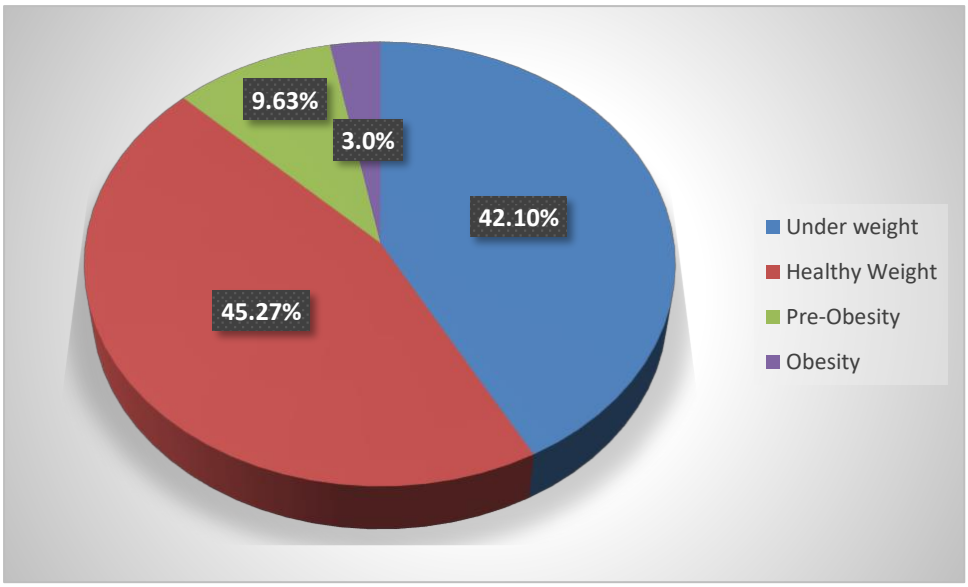


Figure 2: BMI status among participants (N=94)

In most of cases, Polycystic ovary syndrome (PICOS) women's vitamin D level with Fetal bovine serum (FBS) was very low (51.58%). Chai squaretest shows that the association between vitamin D with FBS was not significant (p=.841). The association between vitamin D with BMI was also very low (43.16%) and was not significant p=.381).

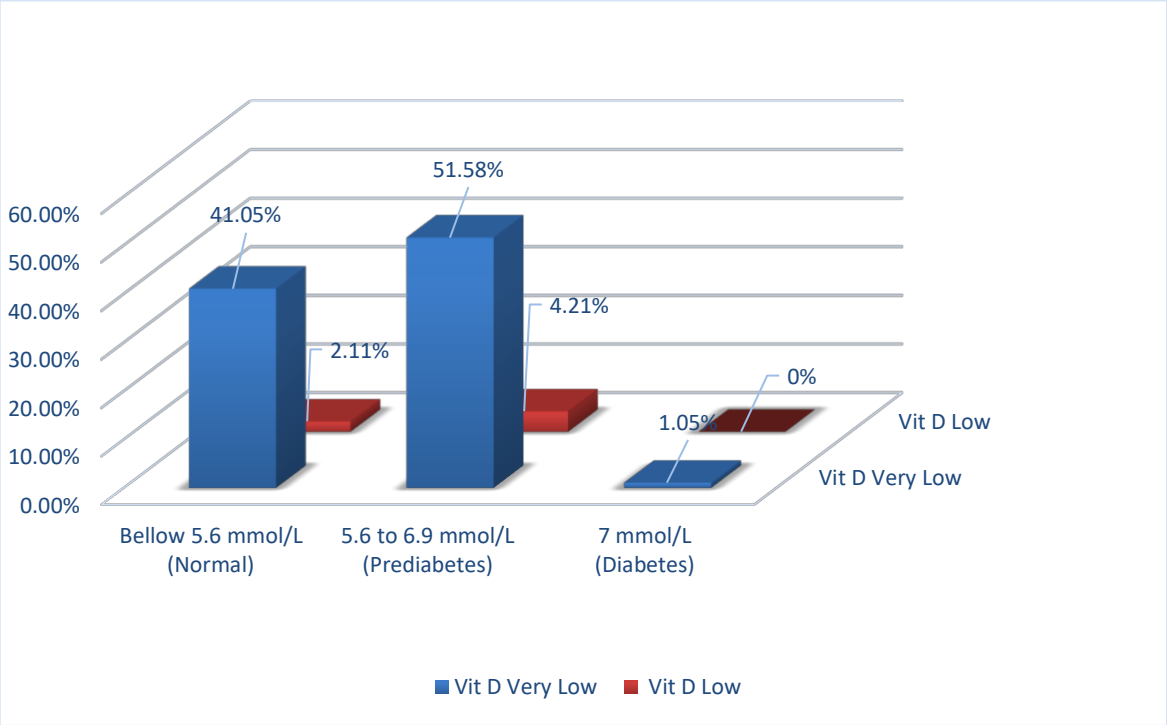


Figure 3: Association between Vitamin D and FBS (N=94)

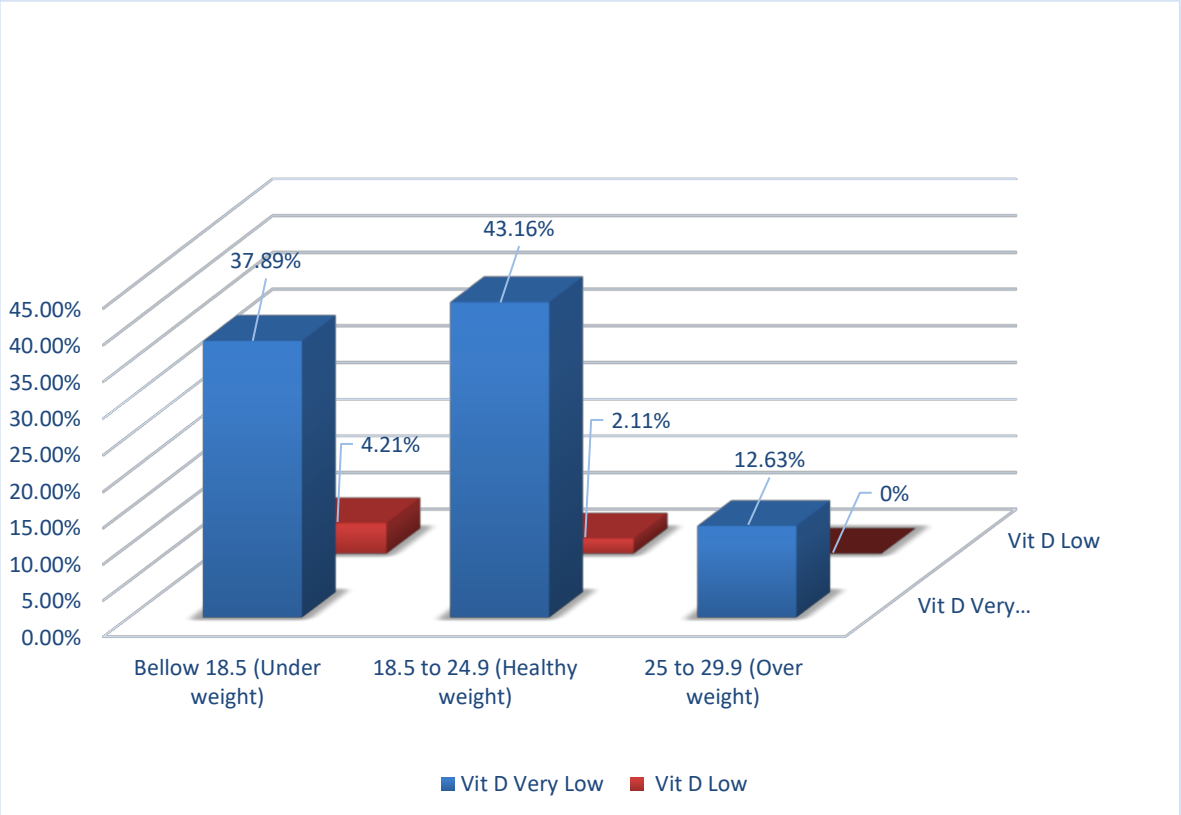


Figure 4: Association between Vitamin D and BMI (N=94)

## 4. Discussion

The cross-sectional study found the frequency of vitamin D deficiency among adolescents with PCOS to be 92.6 %. They also have high insulin resistance and obesity.

Although vitamin D primarily plays a role in bone metabolism, it has important functions in the reproductive system. Vitamin D receptors are found in ovarian and endometrial tissues and play an important role in steroidogenesis. A high prevalence of vitamin D deficiency has been reportedall over India for all age groups including neonates, infants, school-going children, adolescents, adults, pregnant and lactating women, and senior citizens. This is probably a result of poor sun exposure, dark skin complexion, atmospheric pollution, vegetarian food habits, absence of food fortification with vitamin D, and poor intake of vitamin D supplements. Garg et al. did a study in 2015 (India) where Vitamin D deficiency was observed in 92.8% of all PCOS patients while the rest had vitamin D insufficiency (≥30 ng/mL) (Kokila et al., 2017).

Mazloomi S et al in their study have reported low levels of vitamin D in women with PCOS, withaverage vitamin D (25-OHD) levels between 11-31 ng/mL, and the majority having values<20 ng/mL (67–85%) which is comparable to our study. Apart from other risk factors, PCOS itself wasfound to be associated with decreased vitamin D levels, which is similar to our study. In the presentstudy, among 94 total cases of PCOS, the mean age was 15.34±1.91 years. Age ranged from 12 years to 18 years. Many studies have reported inverse associations between body weight (BMI, body fat, and waist measurements) and serum 25-OHD levels in women with PCOS, with reportsof levels 27–56% lower in obese women with PCOS, compared to non-obese women with PCOS.A recent study in women with PCOS also found low 25-OHD levels were significantly determinedby the degree of adiposity (BMI and total fat mass) and were not directly affected by the development of insulin resistance (Ardabili et al., 2012). Consequences of vitamin D deficiency include a broad range of health problems. A lack of vitamin D has been linked to an increased likelihood of developing life-threatening malignancies, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus (Michael, 2004). It has been proposed because of the association betweenlow sun exposure and the development of many internal malignancies, the incidence, and mortalityfrom these cancers could be prevented if adequate vitamin D blood level is maintained. Hence, the importance of screening of those at risk especially obese with BMI of ≥35 provided that cost- effective analysis is considered. The adolescent girls with PCOS had fasting insulin levels (<20uIU/ml) among 14.9% of PCOS. On other hand, high fasting Insulin level (>20uIU/ml) among 85.1% of PCOS. Insulin sensitivitymay not be influenced by circulating 2 5(OH) vitamin D in some populations. The associations of 25(OH) D with insulin sensitivity (determined with a euglycemic-hyperinsulinemic clamp) in morbidly obese Caucasian women. Serum 25(OH) D was not associated with insulin sensitivity in these subjects either before bariatric surgery or 5- and 10- years post-surgery suggesting that they found low serum 25(OH) D concentrations before and afterbariatric surgery do not negatively affect insulin sensitivity (Manco, 2010).

In the present study BMI 28.31±4.46 kg/m2, Insulin 22.07±4.23 µIU/ml, FBS 6.88±1.56 mmol/L,and HOMA-IR 6.98±1.79. Some biochemical and hormonal data are presented in Table. Only 2 (2.1%) women were in the normal limits of vitamin D levels as ≥30 ng/ml. The mean value of vitamin D was 12.9 (4.2-31.4). In the study conducted by Setenay Arzu Yılmaz, the mean VitaminD level of the lean PCOS cases was 16.52 ng/ml. In patients with PCOS, vitamin D levels were found too below.

In our study total 94 PCOS patients with vitamin D deficiency 80 (85.1%) participants had markers of insulin resistance like acne, hirsutism, acanthosis nigricans. Among patient's with irregular menstruation was 94 (100%), Lower abdominal Pain 35 (37.2%), Hirsutism 63 (67.0%).

Under Normal BMI 23 (24.5%), Overweight 45(47.9%) and Obese 26 (27.7%). In addition, adviceon diet and lifestyle modification was also instructed. Other insulin sensitizers like Myo-inositol,D-chiro inositol, berberine were not used in any of these patients. In patients with vitamin D deficiency, we had supplemented them with Injection Vitamin D, 6 Lakh IU has given intramuscularly, 2 doses 6 weeks apart, and in those with insufficiency oral vitamin D supplementation was given in the form of 60,000 IU, once a week for 8 weeks and thereafter once a month as maintenance. In all these patients, oral calcium 500 mg tablets were also added once daily. In the

patients with insulin resistance and obesity, metformin 500 mg tablet was given in theoral form. In addition, advice on diet and lifestyle modification was also instructed.

This is a significant observation. Our study can be compared to the study done by Thys-Jacobs S et al where the aim of their study was to determine whether vitamin D and calcium dysregulationcontribute to the development of follicular arrest in women with PCOS, resulting in reproductive and menstrual dysfunction. Vitamin D repletion with calcium therapy resulted in normalized menstrual cycles within 2 months for seven women, with two experiencing resolutions of their dysfunctional bleeding. Two became pregnant, and the other four patients maintained normal menstrual cycles (Kokila et al., 2017). Many studies have reported inverse associations between body weight (BMI, body fat, and waist measurements) and serum 25-OHD levels in women withPCOS, with the report of levels 27–56% lower in obese women with PCOS, compared to non- obese women with PCOS (Rebecca, 2012).

A recent study in women with PCOS also found low 25-OHD levels were significantly determined by the degree of adiposity (BMI and total fat mass) and were not directly affected by the development of insulin resistance (Kokila et al., 2017). Thus, Vitamin D deficiency is common in patients of PCOS, both lean and obese. Supplementation with Vitamin Dand Calcium can improve the menstrual disorders associated with PCOS and with a favorable reproductive outcome. However, our study has its limitations in the small sample size. More randomized controlled studies with a large number of patients will confirm the potential benefits of Vitamin D supplementation in PCOS patients.

## 5. Conclusion

The majority of adolescent females who have PCOS have an insufficient level of vitamin D, and the prevalence of obesity is also rather high. It is extremely likely that the findings of this study will contribute to a better understanding of how PCOS is managed, and patients will benefit individually from having a better grasp of how to manage their condition. The results of this study brought the true image of insulin resistance and metabolic syndrome among diverse phenotypes of women with PCOS in Bangladesh. The clinician may be able to manage cases of obesity in teenagers with PCOS more effectively if they estimate vitamin D levels and examine the level of obesity in the patient.

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**Funding**: Not applicable.

**Conflict of Interest**: The authors declare no conflict of interest.

**Informed Consent Statement/Ethics Approval**: Not applicable.

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# Capsule Dosage Forms Containing Natural Antioxidant Microcapsules of Cantigi Extract

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**Abstract**
Microencapsulation technology in product development of the food, beverage, and health sectors may provide innovative products with better stability, functionality, and prolonged releases. This study aims to formulate capsule dosage forms containing natural antioxidant microcapsules of Cantigi extract and analyze slow-release profiles. Three microcapsule formulations (F1, F2, and F3) were made by solvent evaporation method using ethyl cellulose coating and characterized for color, odor, particle size, shape, recovery, moisture content, encapsulation efficiency, drug loading, density, and antioxidant activities. Then, three capsule dosage forms (FI, FII, and FIII) of microcapsules of the most potent antioxidant activity, microcrystalline cellulose, and colloidal silicon dioxide. The results showed that the most potent microcapsules were F1, while the most potent capsule dosage forms were FIII. FIII provides the slowest release compared with FI and FII. By analyzing the kinetics of FIII using zero-order, first-order, Higuchi, and Kosmeyer-Peppas models, the release profile of FIII is the best fit with the first-order model kinetics, consistent with a previous study. Moreover, all capsule dosage forms have a biphasic slow-release profile for 60 minutes. The conclusion is that this study can prepare hard-gelatin capsule dosage forms containing natural antioxidant microcapsules of cantigi extract with first-order and biphasic slow-release profiles.

**Keywords:** Cantigi Extract, Capsule Dosage Forms, Microencapsulations, Release Profiles

## 1. Introduction

The uses of natural ingredients in medicinal preparations worldwide have increased over time as many drug manufacturers are starting to switch to producing drugs using natural ingredients. The advantages of use may provide affordable prices, fewer side effects, and cure not only one of the symptoms or diseases but also improve physiological function in the body (Kurek et al., 2022).

One of the plants that may be a source of natural medicines is Cantigi (Vaccinium varingiaefolium (Blume) Miq.) from the Ericaceae family growing well near volcanic craters. Cantigi is part of the same genus of Vaccinium as Bilbery (Vaccinium mystillus), which has been well-known worldwide. The empirical uses of Cantigi are anti-inflammatory, antispasmolytic, and antihypertensive. A previous study showed that Cantigi extract has a very potent antioxidant activity ($IC_{50}$ <20 ppm) (Kosasih et al., 2021).

Cantigi leaves contain flavonoids, steroids, tannins, triterpenoids, saponins, and steroids (Kosasih et al., 2022). They have two kinds of color; the young are red, and the old are green. Generally, plants having red or purple colors contain anthocyanin compounds, which are potent antioxidants (Kosasih et al., 2021). Previous research using GC-MS method, cantigi leaves contain 33 compounds, some of which have potential as antioxidants, namely hexamethyl cyclotrisiloxane, 5-(thiopen-2-yl) methyl-2H-tetrazole, hexadecanoic acid methyl ester, 9-octadecenoic acid (Z), beta-mono-olein, 1,2-benzenedicar-boxylic acid, mono(2-ethylhexyl) ester, and friedelin (Kosasih et al., 2020).

Antioxidants may neutralize free radicals and protect the body from degenerative diseases such as cancer, heart disease, arthritis, cataracts, diabetes, and liver disease. They can destroy a reaction chain of free radical formation by donating H-atoms, reducing the concentration of reactive oxygen, reducing free radicals at the initiation stage, and chelating transition metal catalysts (Yamauchi et al., 2024).

Microencapsulation is a process of enclosing micron-sized particles in a polymeric shell, or by which the small particles or droplets are coated with a coating or encased in a homogeneous or heterogeneous matrix and created to give small capsules (Jyothi et al., 2012). It protects micron-sized sensitive substances from the external environment and provides controlled release. It may contain liquids or solids with sizes ranging from 33 nm – 20 μm (Abbaspoor et al., 2012). The principle of microencapsulation is to mix a core phase, water phase, and coating phase until a stable emulsion forms, then proceed with an attaching process of the coating material to the surface of the core substance and the particle reduction process (Yan et al., 2024). Several advantages of microcapsule formulations include masking the bitter taste of drugs, regulating the drug release site, improving drug release properties, reducing undesirable drug reactions and side effects, extending shelf-life, enabling drug delivery at specific locations, and enabling controlled and sustainable medicinal compounds (Paulo et al., 2017). According to previous research, ethanol extract from cantigi leaves has a pH of 2.87 (acid), so it has the potential to irritate the stomach (Kosasih et al., 2021). Therefore, microencapsulating cantigi extract may protect the gastric mucosa while maintaining antioxidant activity caused by unfriendly gastrointestinal conditions. In microcapsule formulations, a coating aims to protect the core substance, which is non-toxic and does not react with the extract. In other words, polymers will layer active substances (Mariel et al., 2022). Coatings for microcapsules may use a combination of polymers, such as ethyl cellulose, cellulose derivatives, chitosan, alginate, and other polymers (Raj et al., 2024; & Singh et al., 2010). In this microcapsule formulation, the coating polymer is ethyl cellulose. Ethyl cellulose is water-insoluble but soluble in various organic solvents, odorless, colorless, tasteless, and stable. Some reasons for choosing ethyl cellulose are: Non-toxic, biocompatible, safe for consumption, maintains the stability of the core ingredient (active substance) well, and masks the unpleasant taste of medicinal ingredients (Murtaza, 2012). There are several microencapsulation methods, including spray-drying, spray-congealing, freeze-drying, solvent evaporation, coacervation, and interfacial polymerization. This study uses the solvent evaporation method by which the active substance is suspended in a polymer solution containing an anhydrous organic solvent and then evaporated (Ahangaran, 2022).

After microencapsulation, microcapsules are mixed with other excipients and filled into gelatin capsules. The advantages of Capsule formulations include maintaining the stability of the microcapsules that function as antioxidants, covering unpleasant tastes and odors, and making them easier to consume as an oral preparation because of their small size and smoother surface (Janczura, 2022). The DPPH method is the most common antioxidant testing, where antioxidant activity is analyzed using the DPPH (1,1-diphenyl-2-picrylhydrazyl) reagent. The advantage of this method is that it is simple, easy, fast, inexpensive, and sensitive for samples with small concentrations (Kosasih et al., 2020).

Based on the previous information, this study aims to formulate capsule dosage forms containing natural antioxidant microcapsules of cantigi extract and analyze their release profiles.

## 2. Materials and Methods

### *2.1 Materials*

The Cantigi leaves are from the White Crater, Mount Patuha in Bandung, Indonesia, identified at the Herbarium Depokensis (UIDEP), Department of Biology, Faculty of Mathematics and Natural Sciences, University of Indonesia. Other materials used are analytical or pharmaceutical grade.

*2.2 Methods*

2.2.1 Preparation and Characterization of Cantigi Extract

Cantigi extraction used a kinetic maceration method with a ratio of 1:10 (dry powder simplicia: 70% ethanol) for 6 hours. The concentration of the extract used a rotary evaporator at 45˚C, and the characterization of the thick extract obtained includes organoleptic (color, odor, appearance), pH, solubility, moisture content, antioxidant activity, phytochemistry, and heavy metal content (Yulyana et al., 2016; & Hibrah et al., 2022).

2.2.2 Synthesis and Characterization of Microcapsules

Synthesis of three microcapsule formulations used the below compositions: Cantigi extract (1 g), ethyl cellulose (F1: 1, F2: 2, and F3: 3 g), acetone (30 mL), liquid paraffin (60 mL), tween 80 (0.78 mL), and n-hexane (qs). The ratios of the core substance (cantigi extract) and the coating (ethyl cellulose) were F1 (1:1), F2 (1:2), and F3 (1:3). With stirring, dissolved ethyl cellulose in 30 mL of acetone. Cantigi extract was dispersed and stirred for 20 minutes. In another beaker, 60 mL of liquid paraffin and 0.78 mL of tween 80 were mixed to make a vehicle phase and continued to stir. An emulsion was made by pouring drop by drop the mixture of coating solution and cantigi extract dispersion to the vehicle phase, stirred at 850 rpm and room temperature for 2.50 hours until all the acetone evaporated. After microcapsules formed, filtered, washed three times with n-hexane, and dried in an oven for 2 hours at 40-50˚C (Song et al., 2022; Brlek et al., 2021; & Yasin et al., 2021). Characterizations of microcapsules include organoleptic (color, odor, shape), recovery, moisture content, entrapment efficiency, drug loading, particle size distribution, bulk and tapped density (Raj et al., 2024; Hibrah et al., 2022; Ditjen Farmalkes, 2022; Song et al., 2022; & Choudhury et al., 2021), and antioxidant activity (Yamauchi et al., 2024).

2.2.3 Capsule Dosage Forms Containing Microcapsules of Cantigi Extract

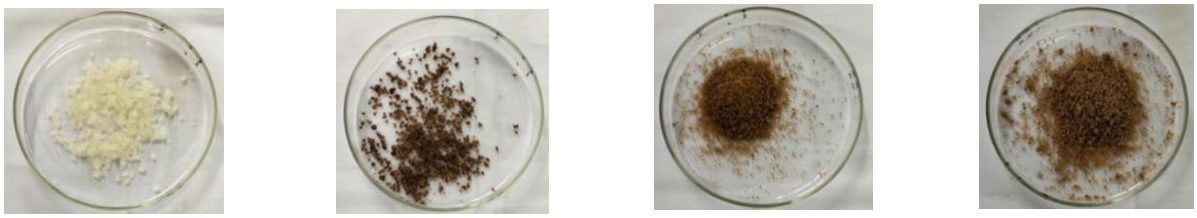
Capsule dosage forms (FI, FII, and FIII) contain microcapsules (10, 20, and 30 mg each), colloidal silicon dioxide (2.32, 2.24, and 2.16 mg each), microcrystalline cellulose PH 102 (add to 300, 300, and 300 each). The total weight per capsule is 300 mg. Capsule mass was made by mixing all components and filling into #2 hard-gelatin capsules. Before filling into hard gelatin capsules, the capsule mass was characterized for moisture content (USP <921>, 2023), particle distribution (USP <786>, 2023), bulk density (USP <616>, 2023), tapping density (USP <616>, 2023), Carr's index, Hausner ratio, and flowability (USP <1174>, 2023). After filling into hard gelatin capsules, the resulting capsules were examined for mass uniformity, disintegration time, and release profile (Šedbarė, 2023).

**3. Results**

Table 1: Characteristics of specific and non-specific parameters of Cantigi extract

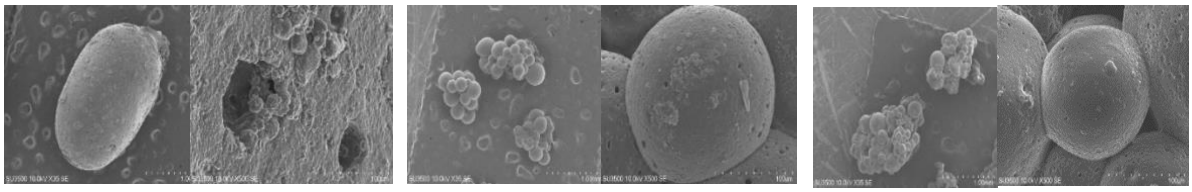
| Test parameters | Results |
|---|---|
| Organoleptic: Color | Dark brown |
| Odor | Cantigi specific |
| Appearance | Thick |
| pH | 4.30±0.01 |
| Solubility: in methanol | Soluble |
| in ethanol 96% | Soluble |
| in DMSO | Freely soluble |
| in purified water | Soluble |
| Moisture content (%) | 8.67±1.56 |
| Antioxidant activity ($IC_{50}$, ppm) | 17.40±1.00 ppm (Cantigi extract) |

| | |
|---|---|
| | 2.75±0.040 ppm (Vitamin C, control) |
| Phytochemistry: | Alkaloids: + Saponins: + Tannins: + Phenolics: + Flavonoids: + Steroids: - Triterpenoids: + Glycosides: + |
| Heavy metal content: Pb | Undetectable |
| Cd | Undetectable |



(a) (b) (c) (d)

Figure 1: Four different physical forms of microcapsules containing Cantigi extract. Microcapsules of F0 (a), F1 (b), F2 (c), and F3 (d).



(a) (b) (c)

Figure 2: Shape (morphology) of microcapsules generated by an SEM. (a) = F1, (b) = F2, and (c) = F3.

Table 2: Characteristics of Microcapsules containing Cantigi extract

| No | Parameters | F1 | F2 | F3 |
|---|---|---|---|---|
| 1 | Odor | Specific Cantigi | Specific Cantigi | Specific Cantigi |
| 2 | Color | Dark brown | Light brown | Light brown |
| 3 | Shape | Powder | Powder | Powder |
| 4 | Recovery (%) | 77.66±0.15 | 91.74±0.24 | 87.91±0.01 |
| 5 | Moisture content (%) | 3.67±0.34 | 8.67 ± 0.09 | 5.10 ±0.10 |
| 6 | Entrapment efficiency (%) | 73.18±0.33 | 83.86±0.26 | 83.84±0.01 |
| 7 | Drug loading (%) | 64.00±0.19 | 36.31±0.12 | 28.29±0.00 |
| 8 | Particle size (μm) | 0.1067 | 0.2614 | 0.2455 |
| 9 | Bulk density (g/mL) | 0.31±0.00 | 0.24±0.00 | 0.24±0.00 |
| 10 | Tapped density (g/mL) | 33±0.00 | 0.25±0.00 | 0.25±0.00 |
| 11 | Compressibility index (%) | 4.67±1.16 | 2.61±0.00 | 2.27±0.39 |
| 12 | Antioxidant activity (IC50, ppm)<br>Week-0<br>Week-4 | <br>19.3±0.28<br>22.75±0.52 | <br>27.19±1.12<br>33.94±0.80 | <br>44.92±0.91<br>49.38±1.66 |

Table 3: Characteristics of capsule masses of FI, FII, and FIII containing microcapsules

| No | Parameters | FI | FII | FIII |
|---|---|---|---|---|
| Capsule masses | | | | |
| 1 | Flow property (Direct method), g/s | 2.10±0.26<br>Cohesive | 2.27±0.11<br>Cohesive | 2.12±0.38<br>Cohesive |
| 2 | Flow property (Indirect method), α° | 19.96±1.06<br>Excellent | 18.60±0.29<br>Excellent | 19.44±1.63<br>Excellent |
| 3 | Particle size distribution<br>(# Mesh; % weight) | <br>20; 0<br>20/40; 1,14<br>40/60; 1,50 | <br>20; 0<br>20/40; 0<br>40/60; 0.8 | <br>20; 0.33<br>20/40; 1.06<br>40/60; 2.85 |

| | | | | |
|---|---|---|---|---|
| | | 60/80; 5,68<br>80/100; 41,73<br>100/120; 40,92<br>120; 9,02 | 60/80; 7.2<br>80/100; 33.6<br>100/120; 37.6<br>120; 20.8 | 60/80; 14.66<br>80/100; 35.48<br>100/120; 30.39<br>120; 15.23 |
| 4 | Moisture content (%) | 5.81±0.45 | 5.73±0.43 | 5.30±0.14 |

Table 3: Characteristics of capsule dosage forms of FI, FII, and FIII containing microcapsules

| No | Parameters | FI | FII | FIII |
|---|---|---|---|---|
| Capsule dosage forms | | | | |
| 1 | Cap. weight average deviation (mg) | 2.32±1.30 | 3.15±2.12 | 1.36±0.92 |
| 2 | Disintegration time (min.) | 5.38 | 6.07 | 7.19 |
| 3 | Antioxidant activities (ppm) | 79.76±5.58 | 57.36±1.40 | 49.29±0.25 |
| 4 | Extract release of capsules<br>(Time (min): % release) | 5: 19.89±0.62<br>15: 30.31±1.84<br>30: 36.30±2.09<br>45: 51.94±4.53<br>60: 66.36±1.39 | 5: 13.21±0.15<br>15: 15.48±0.62<br>30: 18.58±0.28<br>45: 26.15±0.93<br>60: 32.77±1.18 | 5: 8.31±0.67<br>15: 10.54±0.18<br>30: 11.16±0.56<br>45: 17.56±0.56<br>60: 21.98±0.16 |
| 5 | Release profile of capsules<br>(5-20% in 60 minutes) | Sustained<br>Not match | Sustained<br>Not match | Sustained<br>Best fit |

Table 4: Analysis of extract release of FIII using model kinetics

| No | Model kinetics | Regression equation | $R^2$ | Conclusion |
|---|---|---|---|---|
| 1 | Zero-order | y = 0.2445x + 6.2915 | 0.9379 | - |
| 2 | First-order | y = 0.0076x + 0.8800 | 0.9577 | Best fit |
| 3 | Higuchi | y = 2.366x + 1.5476 | 0.8642 | - |
| 4 | Kosmeyer-Peppas | y = 0.3616 + 0.6240 | 0.8275 | - |

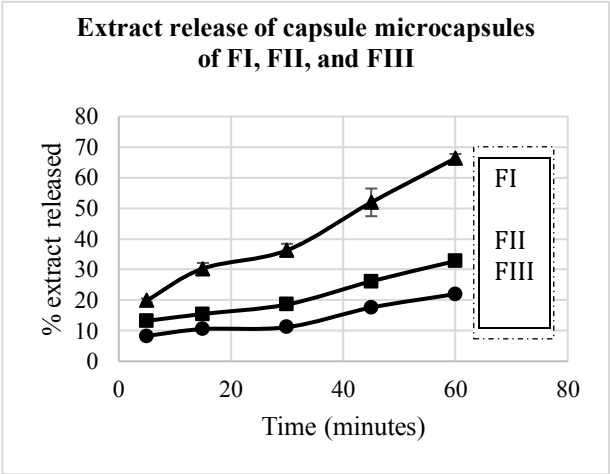



Figure 3: Extract releases in purified water of capsules FI, FII, and FIII.

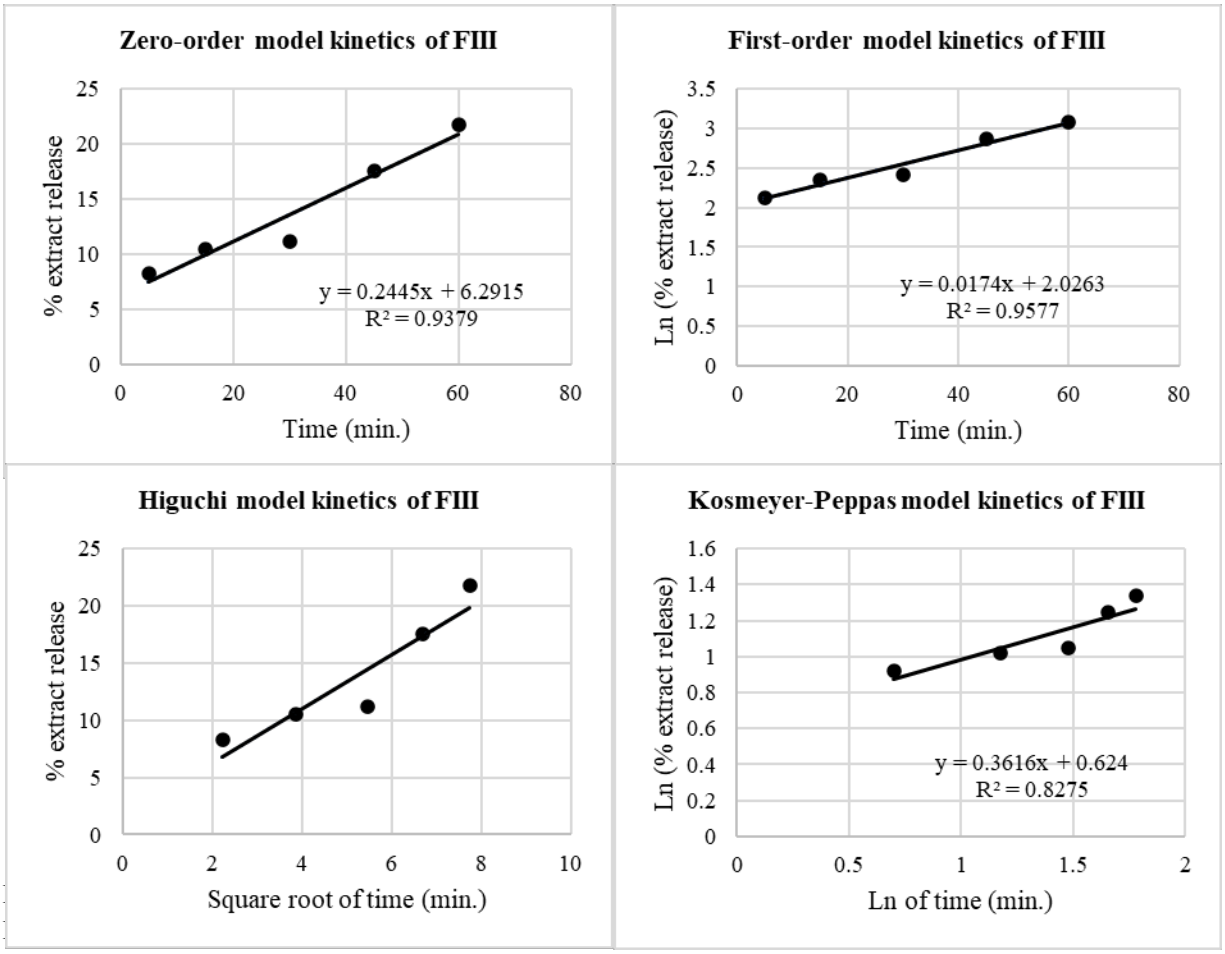



Figure 4: Analysis of extract releases from FIII dosage form using zero-order, first-order, Higuchi, and Kosmeyer-Peppas model kinetics

## 4. Discussion

### *4.1 Preparation and Characterization of Cantigi Extract*

Plant identification is at the Herbarium Depokensis (UIDEP), Department of Biology, Faculty of Mathematics and Natural Sciences, University of Indonesia, and receives a letter of No. 115/UN2.F3.11/PDP.02.00/2023 stating that the leaves used are from the species Vaccinium varingiaefolium (Blume) Miq. of the Ericaceae family. The degree of fineness of simplicia powder showed that 100% of simplicia powder passed through the #4 sieve, and 24.35% of simplicia powder passed through the #18 sieve. The fineness of simplicia powder may affect the number of compounds to extract (Ditjen Farmalkes RI, 2017). Preparation extract using the maceration method of 502.346 grams of dried simplicia powder with 5 liters of 70% ethanol results in a thick extract of 156.9 grams (31.23% and a DER-native of 3.20). A DER-native value shows the amount of starting material (simplicia) used to make a unit of extract (Monagas et al., 2022). Table 1 shows the characteristics of the Cantigi extract consisting of organoleptic (color, odor, and appearance), pH, solubility in several solvents, moisture content, antioxidant activity, phytochemistry, and heavy metal content. All characteristics are parts of specific and non-specific parameters and extract standardization (Ditjen Farmalkes RI, 2017).

The results of the organoleptic examination show that the thick extract of Cantigi leaves was dark brown in color with a characteristic cantigi odor. The pH of the Cantigi extract is 4.3, and the flavonoid content in the extract may cause this low pH extracted by the 70% ethanol solvent. The requirement for the water content of the extract is ≤10%, but the average water content of the extract is 8.67%. Water content above 10% may cause microbial contamination. The antioxidant activity tests use the Cantigi extract and vitamin C (as a control) and the DPPH method. Both results show potent antioxidant activities. This comparison method is to know whether both analyses

of the extract and control are acceptable. The compound group that has a role as natural antioxidants in plants is phenolic compounds. Based on the above phytochemical screening test, one group of natural phenolic compounds is glycosides consisting of flavonoids and tannins. Because of its toxicity, a heavy metal content determination is a requirement. Lead (Pb) and cadmium (Cd) are heavy metals and if they contaminate an extract, there is a high risk of chronic poisoning and weakness. The analysis results show no heavy metal content detected (Ditjen Farmalkes RI, 2017).

*4.2 Synthesis and Characterization of Microcapsules*

Figure 1 shows four different physical forms of microcapsules consisting of the Blank Formula (F0), Formula 1 (F1), Formula 2 (F2), and Formula 3 (F3). The color of the resulting microcapsules (Figure 1 and Tabel 2 of #2) is affected by the amount of ethyl cellulose as the coating agent. The more ethyl cellulose is used compared to the extract, the brighter the color of the resulting microcapsules will be. While, Figure 2 shows the shape (morphology) of microcapsules generated by an SEM. The greater the ratio of ethyl cellulose to extract, the more the core can be coated and become a better round shape, but this results in the microcapsule particles sticking to each other (Monagas et al., 2022).

Table 2 shows the characteristics of Cantigi extract-loaded microcapsules consisting of organoleptic (odor, color, and shape), recovery, moisture content, entrapment efficiency, drug loading, particle size, drug loading, bulk density, tapped density, compressibility index, and antioxidant activity. Table 2 (#4) shows the relatively low recovery value that may be caused by, during the microencapsulation process, the extract is not coated well due to the poor ratio of coating to extract. Or, during the stirring process, coating material sticks to the walls of the beaker (Sulastri et al., 2019). Table 2 (#5) shows the moisture content of microcapsules. The requirement for moisture content in microcapsules is ≤10%. The moisture content values of the three microcapsule formulas meet the specification (Monagas et al., 2022). Higher moisture content may cause microbial contamination. Table 2 (#6) shows the encapsulation or entrapment efficiency of the extract in microcapsules. The greater the ethyl cellulose used in the formulation, the greater the cantigi extract can be encapsulated in the microcapsules (Kurniawan et al., 2017). Table 2 (#7) shows the drug loading of Cantigi extract in microcapsules. The smaller the drug loading value, the smaller the amount of ethyl cellulose used. The more the coating is used, the less the extract can be loaded. Table 2 (#8) shows the average of microcapsule particle sizes. The particle size of microcapsules can be affected by the stirring speed and the concentration of ethyl cellulose (coating), where the faster the stirring speed, the smaller the microcapsules formed, and the more ethyl cellulose used, the larger the particle size will be. In addition, a thing that can affect particle size is that the greater the coating ratio in each formula, the larger the particle size will be (Kurniawan et al., 2017) [31]. Table 2 (#9, #10, and #11) shows the bulk and tapped density of microcapsules. The compressibility index of the microcapsules can be determined and the flow characteristics of the powder according to the Carr compressibility index (CI) can be identified using bulk and tapped density data. If the Ci of powder has a percentage value ≤ 10%, the powder has excellent flow characteristics. The CI values of the three formulas show excellent flow characteristics. Table 2 (#12) shows the results of the microcapsule antioxidant activity test using the DPPH Method. The $IC_{50}$ value increases from F1 to F3, meaning the IC50 value is affected by the ratio of the core to the coating. Moreover, there is an increase in the $IC_{50}$ value in week 4 for each formula, although the increase is not significant, and the $IC_{50}$ values of each formula at week 0 and week 4 remain in the very potent category of antioxidant activity ($IC_{50}$ less than 50 ppm).

*4.3 Capsule Dosage Forms Containing Microcapsules of Cantigi Extract*

Table 3 shows the characteristics of capsule masses that meet the requirements of flow properties, particle size distribution, and moisture content. Tables 3 of #1 and # 2 show the flow property of capsule mass containing microcapsules of Cantigi extract is based on the direct method and indirect method. If viewed from the flow time alone, the powder flow velocity of the three formulations falls into the cohesive category (1.6-4.0 g/s), but when viewed from the angle of repose value, the powder flow properties are within the excellent category (<25˚). The flow properties of powder are affected by particle size, particle mass weight, and particle shape. The larger the particle size, the smaller the cohesiveness between the particles, which can increase the powder flow rate (USP 46 - NF 41 <616>, 2023; & USP 46 - NF 41 <1174>, 2023). Also, a glidan addition can improve the capsule mass

flow property without a granulation process. Table 3 of #3 shows the particle size distribution of capsule masses of FI, FI, and FIII. The largest particle size is 165 µm in diameter, meaning that most capsule powder consists of fine particles because it does not go through a granulation process. The particle size distribution shows that A wet or dry granulation if carried out, may produce larger particles. Also, the fine is caused by the sizes of microcapsules having small particle sizes of 0.11-0.26 µm. The particle size distribution of capsule mass is carried out using a mesh-screening method. Table 3 of #4 shows the moisture contents of capsule masses of FI, FII, and FIII. All moisture contents meet specification (<10%). The higher moisture contents may promote microbial growth.

Table 4 presents the characteristics of capsule dosage forms of FI, FII, and FIII containing microcapsules. FIII is the best fit with a specification stating that the active ingredient release is within 5-20% in 60 minutes (Kemenkes RI, 2020; & Han et al., 2013). Table 4 of #1 shows the uniformity of capsule weights presented as their capsule deviation. The data meets the standard of weight variation. Table 4 of #2 shows the disintegration times of capsules meeting the specification of less than 15 minutes. Disintegration time is required for the capsule to break into particles and become available in the molecular form when present in body fluids because the drug absorption by the body is in its molecular form. Table 4 of #4 shows the antioxidant activities of capsule formulations determined using the DPPH method. The capsule antioxidant activity test determines whether the excipient addition would affect the antioxidant activity of microcapsules containing Cantigi extract. The addition of excipients does affect the IC50 value of microcapsules handled by adjusting the dose of microcapsules, and the most potent IC50 value is FIII capsules with a 30 g microcapsule dose of cantigi extract.

Figure 3 shows the extract releases in purified water of capsules FI, FII, and FIII, with the FIII being the best fit with a standard of 5-20% release in 60 minutes (Kemenkes RI, 2020). The release profiles provide a biphasic model. Meanwhile, Table 5 and Figure 4 provide the analysis results of the extract releases of FIII using several model kinetics, such the zero-order, first-order, Higuchi, and Kosmeyer-Peppas by comparing the $R^2$ of the linear regression. The first-order model kinetics is the best fit with the R2 of 0.9577. This result is consistent with the previous report (Pinheiro et al., 2007). This result differs from an earlier report using capsules containing gelatin nanoparticles of Cantigi extract. The best fit is the zero-order model kinetics (Kosasih et al., 2024).

## 5. Conclusions

In conclusion, this study can prepare hard-gelatin capsule dosage forms containing natural antioxidant microcapsules of cantigi extract with first-order and biphasic slow-release profiles.

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# Reactogenicity of Primary Vaccination with Hexavalent Vaccines in Infants: Mathematical Projections in Four Southeast Asian Countries

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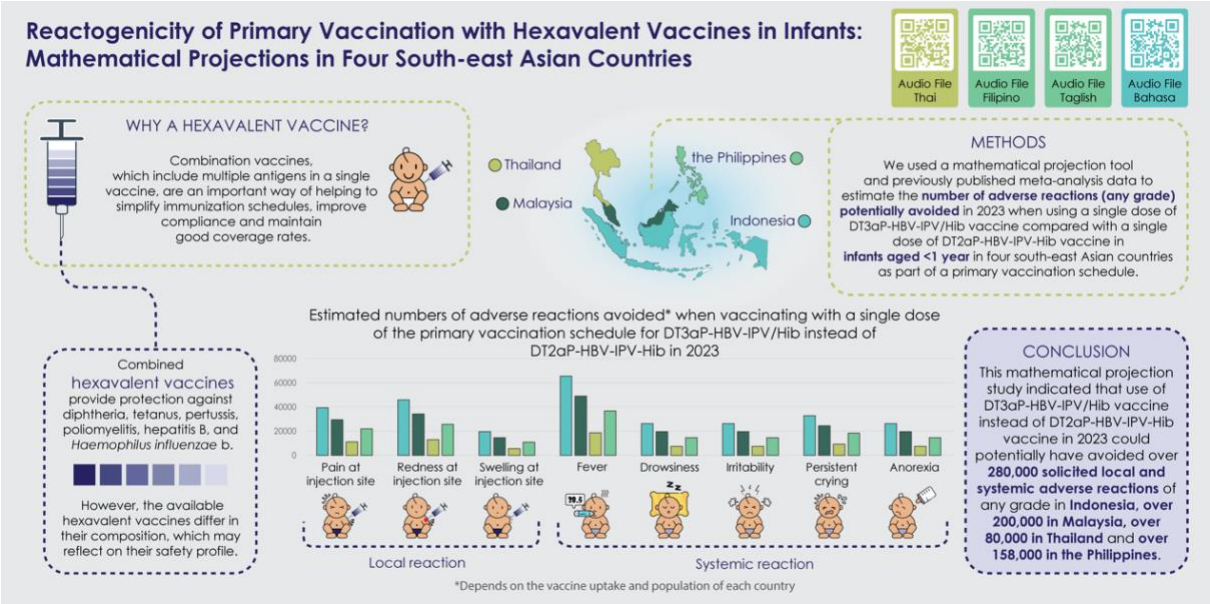
**Abstract**
Hexavalent vaccines against diphtheria (D), tetanus (T), pertussis (P), hepatitis B (HBV), polio (IPV) and *Haemophilus influenzae b* (Hib) are established in the immunization of infants in many countries. A meta-analysis of results from six head-to-head clinical trials comparing two hexavalent vaccines reported that the rate of three local (redness, pain and swelling at the injection site) and five systemic (fever, drowsiness, persistent crying, irritability and anorexia) adverse reactions was lower for the DT3aP-HBV-IPV/Hib vaccine than for the DT2aP-HBV-IPV-Hib vaccine. The objective of this analysis was to compare the impact of adverse reactions after a single dose of the primary series of DT3aP-HBV-IPV/Hib vaccine versus DT2aP-HBV-IPV-Hib vaccine in the infant populations of four countries in Southeast Asia (Indonesia, Malaysia, the Philippines and Thailand). A previously published mathematical projection tool was combined with published data to estimate the number of adverse reactions potentially avoided in 2023 by using DT3aP-HBV-IPV/Hib vaccine compared with DT2aP-HBV-IPV-Hib vaccine. The results indicated that for every 100 infants vaccinated, using DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib would be expected to avoid adverse reactions, ranging from 3 events of swelling at the injection site to 10 events of fever. In 2023, over 280,000 solicited local and systemic adverse reactions of any grade could have been avoided in Indonesia, over 200,000 in Malaysia, over 80,000 in Thailand and over 158,000 in the Philippines. These results could be useful to healthcare decision-makers considering immunization strategies in Southeast Asia.

**Keywords:** Hexavalent Vaccine, Adverse Events, Reactogenicity, Indonesia, Malaysia, Philippines, Thailand




## 1. Introduction

Vaccination against infectious disease is recognized as a highly effective method of reducing mortality and morbidity in children, with an estimated 2.5 million deaths prevented annually in children aged <5 years by use of measles, polio and diphtheria-tetanus-pertussis (DTP) vaccines (Centers for Disease Control Prevention, 2011). The number of recommended routine pediatric vaccinations has increased over time, and recommended vaccination schedules for infants in the United States cover immunization against 14 diseases, including hepatitis B virus (HBV), *Haemophilus influenzae b* (Hib), pneumococcus, rotavirus and rubella (Skibinski et al., 2011). Combination vaccines, which include multiple antigens in a single vaccine, are an important way of helping to simplify immunization schedules, improve compliance and maintain good coverage rates (Koslap-Petraco & Judelsohn, 2008). Hexavalent vaccines, including DTP, Hib, HBV and inactivated poliovirus (IPV), are now established in European vaccination schedules (Obando-Pacheco et al., 2018).

Three hexavalent vaccines are currently available: DT3aP-HBV-IPV/Hib (Infanrix hexa, GSK) (European Medicines Agency, 2021b); DT2aP-HBV-IPV-Hib (Hexaxim [outside Europe] or Hexyon/Hexacima [in Europe], Sanofi Pasteur) (European Medicines Agency, 2021a); and DT5aP-HBV-IPV-Hib (Vaxelis, MCM Vaccine Company) (European Medicines Agency, 2021c). The vaccines have several differences in their composition, including the quantity of diphtheria antigen, the number of pertussis antigens, the HBV and Hib components, and the adjuvant used (Knuf et al., 2021). Vaccine availability varies between countries. In Thailand, Indonesia and the Philippines, the National Immunization Program (NIP) uses a pentavalent vaccine and hexavalent vaccines are available in the private market. In Malaysia, the NIP uses a hexavalent vaccine.

Non-inferiority of the immune responses to the DT2aP-HBV-IPV-Hib and DT5aP-HBV-IPV-Hib vaccines, compared with the DT3aP-HBV-IPV/Hib vaccine, has been demonstrated in randomized clinical trials (RCTs), but the trials did not conduct formal statistical comparisons of safety profiles (Mukherjee et al., 2021). Individual studies indicated a trend towards a higher frequency of local reactions and fever for DT2aP-HBV-IPV-Hib compared with DT3aP-HBV-IPV/Hib, but individual studies may not have sufficient power to determine whether differences are statistically significant. Pooling data from several clinical trials in a meta-analysis can increase the power of the analysis. A systematic literature review and meta-analysis have been conducted to estimate the relative risk of solicited adverse reactions in infants for DT3aP-HBV-IPV/Hib vaccine compared with DT2aP-HBV-IPV-Hib vaccine (Mukherjee et al., 2021). This review extracted data from six head-to-head trials reporting local and systemic reactions after the primary series of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib vaccines in infants. The analysis did not include DT5aP-HBV-IPV-Hib vaccine, as only two trials of this vaccine were

identified in the literature search (Mukherjee et al., 2021). The results of the meta-analysis indicated that the risk of solicited local and systemic reactions was lower for DT3aP-HBV-IPV/Hib vaccine than DT2aP-HBV-IPV-Hib vaccine. The odds ratios (OR) for redness, pain and swelling at the injection site were 0.72 (95% confidence interval [CI] 0.63, 0.83), 0.74 (95% CI 0.62, 0.89) and 0.86 (95% CI 0.74, 0.99), respectively. Regarding systemic reactions, the OR for fever was 0.67 (95% CI 0.54, 0.83), for persistent crying 0.72 (95% CI 0.61, 0.84), for drowsiness 0.82 (95% CI 0.71, 0.94), for irritability 0.82 (95% CI 0.69, 0.98) and for anorexia 0.83 (95% CI 0.72, 0.95) (Mukherjee et al., 2021).

To explore the impact of such differences in reactogenicity profiles, a decision-support tool was developed to investigate the burden of adverse reactions to DT3aP-HBV-IPV/Hib vaccine compared with DT2aP-HBV-IPV-Hib vaccine if implemented in a NIP (George et al., 2023). A previous publication has estimated the potential impact in six countries (Austria, Czech Republic, France, Jordan, Spain and the Netherlands) (George et al., 2023). The objective of the present study was to compare the impact of adverse reactions after a single dose of the primary series of DT3aP-HBV-IPV/Hib vaccine versus DT2aP-HBV-IPV-Hib vaccine in the infant populations of four countries in Southeast Asia, Indonesia, Malaysia, the Philippines and Thailand.

## 2. Methods

### *2.1. Input data*

Data on the incidence of solicited adverse reactions after any vaccine dose in the primary series of vaccinations with DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib vaccines were obtained from a previously published systematic review and meta-analysis (Mukherjee et al., 2021). Eight adverse reactions investigated in this meta-analysis showed a statistically significant difference between the DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib vaccines and were included in the present analysis. These included three local reactions (redness, pain and swelling at the injection site) and five systemic reactions (fever, drowsiness, irritability, persistent crying and anorexia). The input data for these eight adverse reactions used in the present analysis are shown in Table 1 (Mukherjee et al., 2021).

Table 1: Input data for the incidence/proportion of solicited adverse reactions. Adapted from Mukherjee et al. (Mukherjee et al., 2021).

| Parameter | Value [95% Confidence interval (CI)] |
|---|---|
| **1. Pooled incidence/ proportion of adverse reactions for DT2aP-HBV-IPV-Hib** | |
| Pain at injection site, any grade | 0.81 (0.73, 0.87) |
| Redness at injection site, any grade | 0.57 (0.50, 0.64) |
| Swelling at injection site, any grade | 0.40 (0.34, 0.47) |
| Fever, any grade | 0.58 (0.40, 0.74) |
| Drowsiness, any grade | 0.65 (0.54, 0.75) |
| Irritability, any grade | 0.84 (0.75, 0.90) |
| Persistent crying, any grade | 0.78 (0.72, 0.83) |
| Anorexia, any grade | 0.49 (0.41, 0.57) |
| **2. Pooled incidence/ proportion of adverse reactions for DT3aP-HBV-IPV/Hib** | |
| Pain at injection site, any grade | 0.75 (0.69, 0.80) |
| Redness at injection site, any grade | 0.50 (0.42, 0.57) |
| Swelling at injection site, any grade | 0.37 (0.30, 0.44) |
| Fever, any grade | 0.48 (0.36, 0.61) |
| Drowsiness, any grade | 0.61 (0.49, 0.72) |
| Irritability, any grade | 0.80 (0.73, 0.86) |
| Persistent crying, any grade | 0.73 (0.64, 0.81) |
| Anorexia, any grade | 0.45 (0.37, 0.54) |

| **Odds ratio (OR; 95% CI) of this adverse reaction occurring after vaccinating with DT3aP-HBV-IPV/Hib versus vaccinating with DT2aP-HBV-IPV-Hib** | |
|---|---|
| Pain at injection site, any grade | 0.74 (0.62, 0.89) |
| Redness at injection site, any grade | 0.72 (0.63, 0.83) |
| Swelling at injection site, any grade | 0.86 (0.74, 0.99) |
| Fever, any grade | 0.67 (0.54, 0.83) |
| Drowsiness, any grade | 0.82 (0.71, 0.94) |
| Irritability, any grade | 0.82 (0.69, 0.98) |
| Persistent crying, any grade | 0.72 (0.61, 0.84) |
| Anorexia, any grade | 0.83 (0.72, 0.95) |

aP, acellular pertussis; CI, confidence interval; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; OR, odds ratio; T, tetanus

Population projections for the number of infants aged <1 year in 2023 for each of the four countries were obtained from United Nations estimates (United Nations Department of Economic and Social Affairs Population Division, 2022). The estimated eligible populations for 2023 were 4,377,655 for Indonesia, 506,486 for Malaysia, 624,12 for Thailand and 2,451,006 for the Philippines.

Vaccine coverage inputs were 15% in Indonesia (assumption based on current use of hexavalent vaccine in the private sector), 97% in Malaysia (World Health Organization), 30% in Thailand (assumption based on current use of hexavalent vaccine in the private sector), and 15% in the Philippines (based on estimates of immunization through private providers) (Coe et al., 2017).

*2.2. Mathematical projection tool*

A mathematical projection tool was developed using Microsoft Excel 2016 to compare the safety profiles of the hexavalent vaccines DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib. The tool estimated the number of each type of adverse reaction expected for a single dose of each vaccine administered during the first year of life in each of the four countries, by applying the data on proportion of adverse reactions with each vaccine (Table 1) to the number of infants vaccinated in each country in 2023 (calculated from the population data and vaccine coverage data outlined above).

It was assumed that the adverse reaction data from the published meta-analysis (Mukherjee et al., 2021) could be applied to the populations of Southeast Asia. One of the studies included in the meta-analysis was conducted in Thailand, supporting this assumption. Vaccine doses administered after the age of 1 year, combinations of adverse reactions and catch-up vaccination programs were not considered in the analysis.

*2.3. Estimation of absolute risk reduction (ARR)*

The mathematical projection tool calculated the absolute risk reduction (ARR) for each adverse reaction type, defined as the difference between estimated risk of the incidence of an adverse reaction due to DT3aP-HBV-IPV/Hib and risk of the incidence of an adverse reaction due to DT2aP-HBV-IPV-Hib, expressed as a percentage. For each adverse reaction, the mean value of ARR was calculated using the equation:

$$Absolute\ risk\ reduction\ for\ an\ adverse\ reaction, A = \bar{x}_{risk\ of\ A_{DT2aP-HBV-IPV-Hib}} - \bar{x}_{risk\ of\ A_{DT3aP-HBV-IPV/Hib}}$$

The 95% confidence interval for the ARR was calculated by the formula:

$$\pm z * \sqrt{\frac{\sigma^2_{risk\ of\ A_{DT2aP-HBV-IPV-Hib}}}{n_{DT2aP-HBV-IPV-Hib}} + \frac{\sigma^2_{risk\ of\ A_{DT3aP-HBV-IPV/Hib}}}{n_{DT3aP-HBV-IPV/Hib}}}$$

$\sigma^2_{risk\ of\ A_{DT2aP-HBV-IPV-Hib}}$ is the square of the variances of the estimated risk of the incidence of the adverse reaction A due to DT2aP-HBV-IPV-Hib;

$\sigma^2_{risk\ of\ A_{DT3aP-HBV-IPV/Hib}}$ is the square of the variances of the estimated risk of the incidence of the adverse reaction A due to DT3aP-HBV-IPV/Hib;

$n_{DT2aP-HBV-IPV-Hib}$ is the sample size considered for DT2aP-HBV-IPV-Hib;
$n_{DT3aP-HBV-IPV/Hib}$ is the sample size considered for DT3aP-HBV-IPV/Hib;
$z$ =1.96, because a 95% CI is considered

Applying the ARR to a population would give the number of adverse reactions averted by vaccinating with DT3aP-HBV-IPV/Hib versus vaccinating with DT2aP-HBV-IPV-Hib.

### *2.4. Sensitivity analysis*

One-way sensitivity analysis was conducted for the adverse reactions averted for each adverse reaction type. The base-case value was the difference in adverse reactions between DT2aP-HBV-IPV-Hib and DT3aP-HBV-IPV/Hib calculated using the ARR. The parameters used in the sensitivity analysis are summarized in Table 2. For the incidence of adverse reactions with each vaccine and for the ARR, a variation of two standard deviations above or below the base case was used. For vaccination coverage, a variation of 5 percentage points above or below the base-case rate was used, although in Malaysia the base-case coverage was 97% and the maximum value in the sensitivity analysis was 100%.

Table 2: Parameters used in one-way sensitivity analysis

| **Parameters** | **Minimum** | **Maximum** |
|---|---|---|
| Vaccination coverage [a] | -5% | +5% (maximum 100%) |
| Indonesia | 10% | 20% |
| Malaysia | 92% | 100% |
| Thailand | 25% | 35% |
| The Philippines | 10% | 20% |
| Population for 2023 | -10% of population | +10% of population |
| AR incidence/ proportion of DT2aP-HBV-IPV-Hib | -2 SD of mean | +2 SD of mean |
| AR incidence/ proportion of DT3aP-HBV-IPV/Hib | -2 SD of mean | +2 SD of mean |
| Absolute risk reduction | -2 SD of mean | +2 SD of mean |

[a] Vaccination coverage was varied by adding or subtracting 5 percentage points from the base case for each country, subject to a maximum of 100%. In Malaysia the base-case coverage was 97% and therefore the maximum value in the sensitivity analysis was 100%.

aP, acellular pertussis; AR, adverse reaction; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; SD, standard deviation; T, tetanus

## 3. Results

### *3.1. Estimated absolute risk reduction*

The ARR values calculated in this analysis are shown in Figure 1. The number of adverse reactions (of any grade) expected to be avoided for every 100 infants vaccinated by using DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib ranged from 3.0 events of swelling at the injection site to 10.0 events of fever (Figure 1).

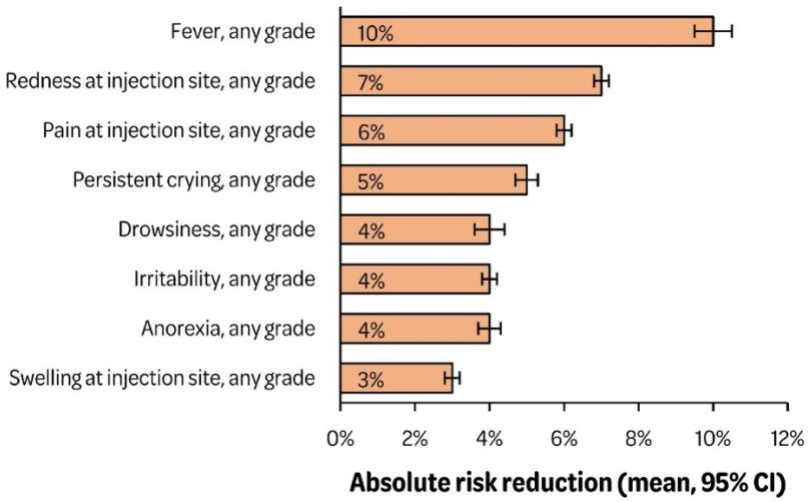



Figure 1: Calculated absolute risk reduction (ARR) for vaccinating with DT3aP-HBV-IPV/Hib versus vaccinating with DT2aP-HBV-IPV-Hib.

aP, acellular pertussis; CI, confidence interval; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

### *3.2. Estimated number of adverse reactions*

The estimated number of each type of adverse reaction after administration of a single dose of DT2aP-HBV-IPV-Hib or DT3aP-HBV-IPV/Hib in each of the four countries in 2023 is shown in Figure 2.

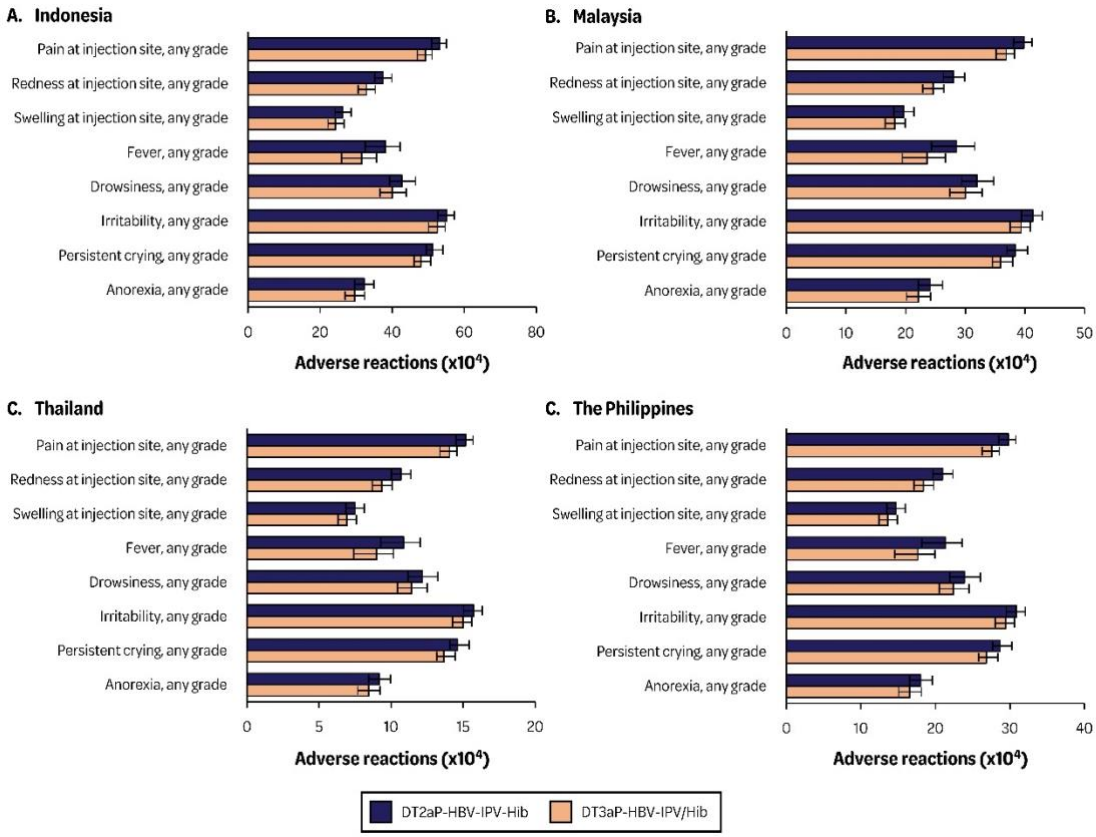



Figure 2: Estimated numbers of adverse reactions when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in (a) Indonesia, (b) Malaysia, (c) Thailand, (d) the Philippines

aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

The estimated number of each type of adverse reaction avoided over a five-year period (2023–2027) by vaccinating with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in each of the four countries is shown in Table 3.

Table 3: Estimated numbers of adverse reactions avoided when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in each of the four countries over five years (2023–2027).

| Year | Estimated number of adverse reactions avoided (any grade) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Pain at injection site** | **Redness at injection site** | **Swelling at injection site** | **Fever** | **Drowsiness** | **Irritability** | **Persistent crying** | **Anorexia** | **Total** |
| **Indonesia** | | | | | | | | | |
| 2023 | 39,398 | 45,965 | 19,699 | 65,664 | 26,265 | 26,265 | 32,832 | 26,265 | 282,353 |
| 2024 | 39,196 | 45,729 | 19,598 | 65,327 | 26,131 | 26,131 | 32,663 | 26,131 | 280,906 |
| 2025 | 39,088 | 45,603 | 19,544 | 65,148 | 26,059 | 26,059 | 32,574 | 26,059 | 280,134 |
| 2026 | 38,978 | 45,475 | 19,489 | 64,964 | 25,985 | 25,985 | 32,482 | 25,985 | 279,343 |
| 2027 | 38,827 | 45,298 | 19,413 | 64,712 | 25,884 | 25,884 | 32,356 | 25,884 | 278,258 |
| Total 2023–2027 | 195,487 | 228,070 | 97,743 | 325,815 | 130,324 | 130,324 | 162,907 | 130,324 | 1,400,994 |
| **Malaysia** | | | | | | | | | |
| 2023 | 29,477 | 34,390 | 14,738 | 49,129 | 19,651 | 19,651 | 24,564 | 19,651 | 211,251 |
| 2024 | 29,358 | 34,251 | 14,679 | 48,930 | 19,572 | 19,572 | 24,465 | 19,572 | 210,399 |
| 2025 | 29,226 | 34,097 | 14,613 | 48,710 | 19,484 | 19,484 | 24,355 | 19,484 | 209,453 |
| 2026 | 29,101 | 33,951 | 14,550 | 48,501 | 19,400 | 19,400 | 24,250 | 19,400 | 208,553 |
| 2027 | 28,960 | 33,787 | 14,480 | 48,267 | 19,306 | 19,306 | 24,133 | 19,306 | 207,545 |
| Total 2023–2027 | 146,122 | 170,476 | 73,060 | 243,537 | 97,413 | 97,413 | 121,767 | 97,413 | 1,047,201 |
| **Thailand** | | | | | | | | | |
| 2023 | 11,234 | 13,106 | 5,617 | 18,723 | 7,489 | 7,489 | 9,361 | 7,489 | 80,508 |
| 2024 | 11,087 | 12,935 | 5,543 | 18,479 | 7,391 | 7,391 | 9,239 | 7,391 | 79,456 |
| 2025 | 10,987 | 12,818 | 5,493 | 18,312 | 7,324 | 7,324 | 9,156 | 7,324 | 78,738 |
| 2026 | 10,936 | 12,758 | 5,468 | 18,226 | 7,290 | 7,290 | 9,113 | 7,290 | 78,371 |
| 2027 | 10,878 | 12,691 | 5,439 | 18,130 | 7,252 | 7,252 | 9,065 | 7,252 | 77,959 |
| Total 2023–2027 | 55,122 | 64,308 | 27,560 | 91,870 | 36,746 | 36,746 | 45,934 | 36,746 | 395,032 |
| **Philippines** | | | | | | | | | |
| 2023 | 22,059 | 25,735 | 11,029 | 36,765 | 14,706 | 14,706 | 18,382 | 14,706 | 158,088 |
| 2024 | 22,123 | 25,810 | 11,061 | 36,871 | 14,748 | 14,748 | 18,435 | 14,748 | 158,544 |
| 2025 | 22,184 | 25,881 | 11,092 | 36,973 | 14,789 | 14,789 | 18,486 | 14,789 | 158,983 |
| 2026 | 22,236 | 25,942 | 11,118 | 37,060 | 14,824 | 14,824 | 18,530 | 14,824 | 159,358 |
| 2027 | 22,292 | 26,008 | 11,146 | 37,154 | 14,861 | 14,861 | 18,577 | 14,861 | 159,760 |
| Total 2023–2027 | 110,894 | 129,376 | 55,446 | 184,823 | 73,928 | 73,928 | 92,410 | 73,928 | 794,733 |

aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

The estimated number of each type of adverse reaction avoided in each country in 2023 by vaccinating with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib is shown in Figure 3.

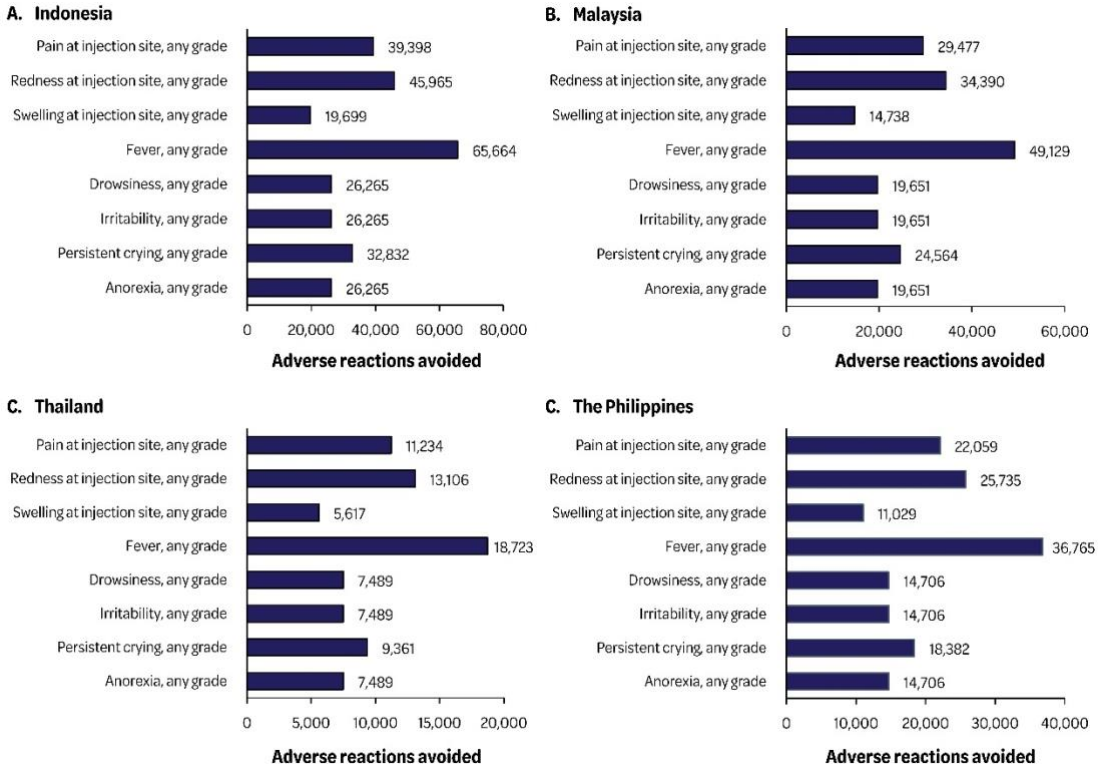



Figure 3: Estimated numbers of adverse reactions avoided when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in 2023 in (a) Indonesia, (b) Malaysia, (c) Thailand, (d) the Philippines.

aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

### *3.3. One-way sensitivity analysis*

The results of the one-way sensitivity analysis for the number of the two most frequent adverse reactions (fever, and redness at the injection site) avoided in 2023 by vaccinating with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib are shown for each of the four countries in Figure 4. The parameters with the most impact on the results were generally the incidence/proportion of adverse reactions with each vaccine, followed by vaccination coverage.

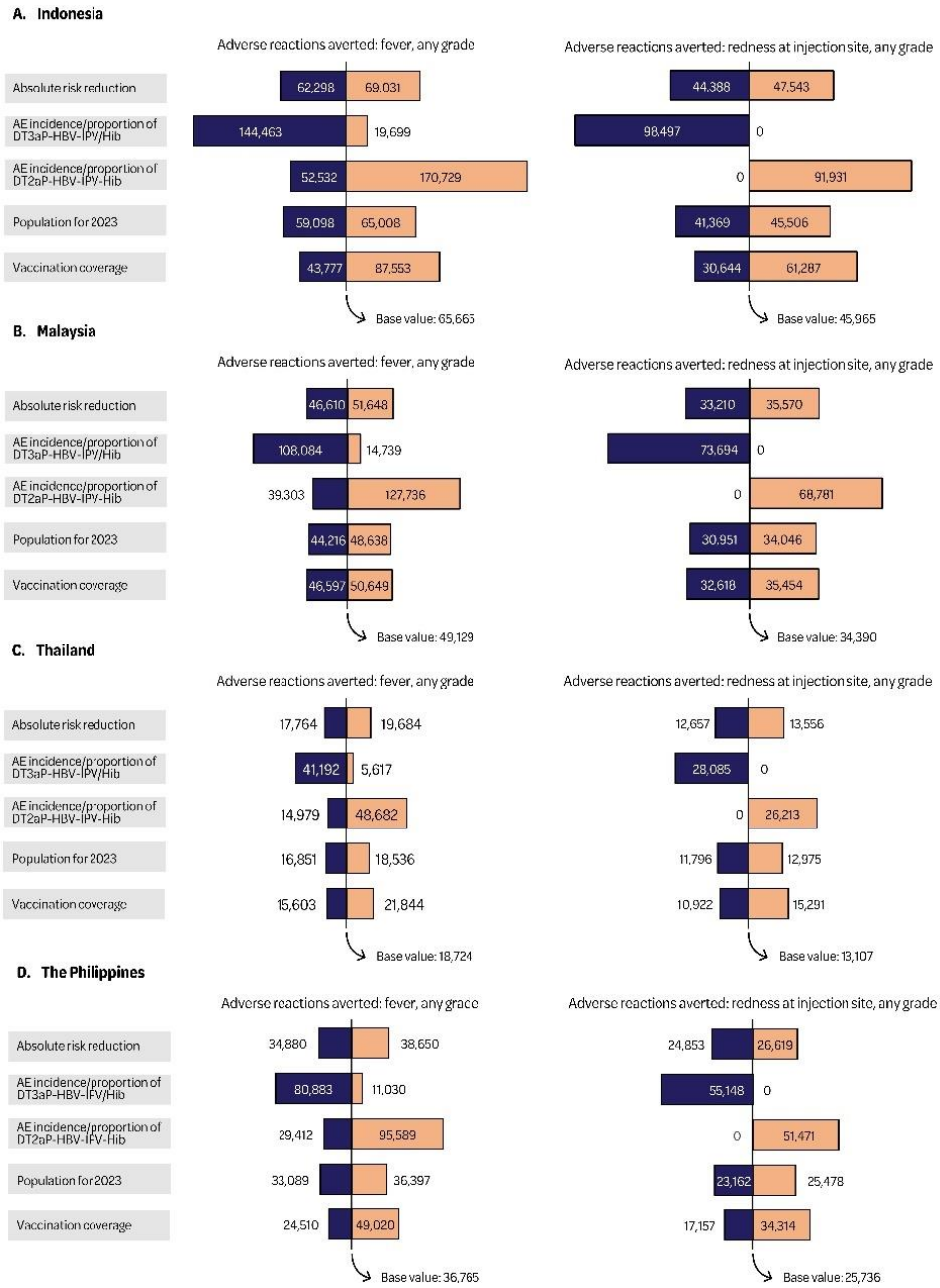



Figure 4: One-way sensitivity analysis on the number of adverse reactions of fever and redness at the injection site avoided when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in 2023 in (a) Indonesia, (b) Malaysia, (c) Thailand, (d) the Philippines.

AE, adverse event; aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, Haemophilus influenzae b; IPV, inactivated poliovirus; T, tetanus

## 4. Discussion

This analysis used a mathematical projection tool to estimate the number of eight different types of adverse reactions after a single dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in infants aged <1 year in 2023 and beyond in four countries in south-east Asia (Indonesia, Malaysia, Thailand and the Philippines). The results indicated that using DT3aP-HBV-IPV/Hib would reduce projected adverse reactions by 3.0–10.0%, compared with DT2aP-HBV-IPV-Hib, i.e., vaccination with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib would be expected to avoid adverse reactions ranging from 3 events of swelling at the injection site to 10 events of fever for every 100 infants vaccinated. The adverse event with the largest differential between the vaccines was fever, followed by redness at the injection site. In 2023, the results indicate that over 65,000 occurrences of fever in Indonesia, over 49,000 in Malaysia, over 18,000 in Thailand and over 36,000 in the Philippines could have been avoided. Taking all eight adverse reactions together, over 280,000 could have been avoided in Indonesia, over 200,000 in Malaysia, over 80,000 in Thailand and over 158,000 in the Philippines.

The study has several strengths. First, it was based on data obtained from a robust systematic literature review and meta-analysis that included RCTs conducted in a broad range of countries (Mukherjee et al., 2021). Second, one of the RCTs included in the meta-analysis was conducted in one of the countries in this analysis (Thailand). Third, the data included adverse reactions of any grade, providing a broad picture of the range of reactions that could affect vaccine recipients and their caregivers.

Nevertheless, this study also has a number of limitations. First, the input data on the incidence/proportion of adverse reactions for each vaccine were derived from a meta-analysis of data from head-to-head RCTs (Mukherjee et al., 2021), as few data from real-world studies are currently available. RCTs are conducted under controlled conditions and may not be representative of the situation encountered in routine clinical practice. However, the acceptable safety profile of DT3aP-HBV-IPV/Hib has been confirmed by analysis of data over ten years of vaccine use in the Australian NIP (Bayliss et al., 2021). Second, vaccine coverage estimates for some of the countries in this study were low, reflecting differences in vaccine availability. For example, some countries have hexavalent vaccines included in the NIP, whereas in others they are available only through the private sector, and some countries include pentavalent vaccines in the NIP with different hexavalent vaccines available through the private sector. Third, the analysis considered only a single dose of vaccine, and so would not capture adverse reactions associated with the other doses in the primary schedule, typically two or three doses, or with any catch-up vaccinations. Therefore, the analysis presented here would be expected to under-estimate the total number of adverse reactions expected from the overall vaccination program. Fourth, the analysis was based on numbers of adverse reactions, and as one infant may experience multiple adverse reactions, the overall number of infants affected by adverse reactions may be lower than the estimated number of adverse reactions. Finally, the third available hexavalent vaccine, DT5aP-HBV-IPV-Hib, was not included in the analysis due to a lack of available data.

Many factors may influence the willingness of parents to have their children vaccinated, including perceptions of individual and community vaccine benefits and perceived vaccine safety (Rosso et al., 2020). Individuals' knowledge, past experiences, perceptions about vaccination, and moral and religious convictions interact with historical, social and political contexts (Aps et al., 2018). In some countries, low rates of vaccination have been associated with outbreaks of vaccine-preventable diseases such as measles and pertussis (Aps et al., 2018). Adverse reactions to vaccine administration may potentially affect parents' willingness to vaccinate their children. A systematic review of factors affecting vaccine uptake in young children found that 'not perceiving vaccines to cause adverse effects' was one of the factors associated with vaccine uptake (Smith et al., 2017). A mother's first vaccination experience with a baby can have an important influence on maternal attitudes to vaccination; for example, feeling that the baby was hurt or experiencing the baby crying after vaccination may lead to concerns about vaccine safety that may in turn contribute to under-vaccination of the child (Betsch et al., 2018). In a study of 506 mothers in Jordan, 39.2% of the mothers agreed that vaccines cause side effects, and 14.6% agreed that they did not offer vaccination to their children because of injection-associated pain (Masadeh et al., 2014). Lower

vaccine coverage could reduce the substantial direct and indirect benefits associated with vaccination (Barnighausen et al., 2011).

Adverse reactions to vaccination can be directly associated with healthcare resource utilization and economic costs, although these may be difficult to estimate. For example, a child experiencing fever after vaccination may need to visit a healthcare professional, and/or one or both of the parents may need to take time away from work to care for the child. A study using data from the United Kingdom (UK), Canada and the Netherlands attempted to estimate the cost of adverse reactions following measles immunization (Carabin et al., 2002). The average cost per vaccinee was estimated at United States dollars (US$)1.55 (95% CI 0.28, 4.35) in the Netherlands, US$2.08 (95% CI 0.48, 5.52) in the UK and US$1.58 (95% CI 0.41, 4.15) in Canada, with fever accounting for 87%, 88% and 84% of the total, respectively (Carabin et al., 2002). A vaccine with a lower frequency of adverse reactions could reduce costs, and potentially help to reduce vaccine hesitancy among parents and support improved vaccine coverage.

## 5. Conclusion

The results of this analysis using a mathematical modelling approach and published data indicate that primary vaccination of infants with DT3aP-HBV-IPV/Hib would be expected to be associated with fewer adverse reactions than vaccination with DT2aP-HBV-IPV-Hib in four countries in Southeast Asia. These results will be valuable to healthcare decision-makers considering immunization strategies in Southeast Asia.

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# Hospital Preparedness of the Gatot Soebroto Army Central Hospital and Indonesia's Level 2 Army Hospital in Facing the COVID-19 Pandemic

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**Abstract**
As an archipelagic nation, Indonesia is at risk of natural disasters, including the possibility of emergency infectious diseases. The worldwide health system is under tremendous strain as a result of the COVID-19 pandemic. Therefore, hospitals spearheading services are critical in preparing to tackle the COVID-19 pandemic. The Indonesian Army Hospital is the primary subject of this study, which attempts to assess hospital preparedness in facing the COVID-19 pandemic. Methods: Our study was a cross-sectional and quantitative analysis of the World Health Organization's 12-item rapid checklist of hospitals' preparedness for COVID-19 from January 2020 to December 2022. This checklist formed the basis of this study's preparation assessment. Data was obtained from 15 people who assessed Army Hospitals from Sumatra to Papua provinces. Hospital preparedness is evaluated using the Preparedness Information System. Result: Every three months, hospital participants had to practice completing a hospital preparedness checklist. The hospital encountered a challenge when manually entering data into the checklist. The results of this study showed that the preparedness of Army hospitals in Indonesia ranges from moderate/medium preparedness degree (if the fulfillment rate is 50-79%) to adequate/high preparedness degree (if the fulfillment rate is more than 80%). Conclusion: Even though meeting the World Health Organization's 12-item rapid checklist of hospitals' preparedness for COVID-19 is tricky, good and continuous cooperation and coordination with the supra system makes it helpful for leaders and health professionals to make policies regarding hospital preparedness to face COVID-19.

**Keywords:** World Health Organization, Army Central Hospital, World Health Organization, Pandemic, Indonesia Army Hospitals, Covid-19, Hospital Preparedness Checklist

## 1. Introduction

### *1.1 Introduce the Problem*

On March 11, 2020, the World Health Organization (WHO) announced the new coronavirus (COVID-19) outbreak as a global pandemic. WHO Director-General Dr. Tedros Adhanom Ghebreyesus said during a news conference that the number of countries and cases outside China has increased by three and thirteen times in the previous two weeks. There will likely be more rises. He asked countries to act right away to limit the virus, declaring that the frightening rates of severity and spread and the alarming rates of inaction have the WHO "deeply concerned." He said, "We should double down." "Our aggressiveness needs to increase" (WHO, 2020).

President Joko Widodo officially declared COVID-19 as a national disaster. The Republic of Indonesia Number 12 of the 2020 Presidential Decree (Keppres) decided to designate non-natural disasters related to the spread of COVID-19 as national disasters (BNPB, 2020). Many people in Indonesia still believe in misinformation about COVID-19 (origin, transmission, and preventive measures). The diverse educational and cultural backgrounds of society mean that misinformation continues to grow; even though correct information has been disseminated many times, misinformation is still growing. Errors in receiving information due to incorrect protocols and preventative measures can contribute to Indonesia's rising COVID-19 case transmission (Nasir NM et al., 2020). As of April 24, 2020, 2,626,321 individuals worldwide have tested positive for the virus; in China, there have been 2,239 fatalities and 75,569 recorded cases (Livingston E et al., 2020).

Additionally, there was a spike in COVID-19 cases in Indonesia. On March 2, 2020, Indonesia announced its first COVID-19 case; by May 8, 34 provinces had recorded over 12,776 cases and 930 deaths. Still, modeling studies suggest that about 2 percent of infections have been documented (Unicef, 2020).

Many people continue to doubt Indonesia's original record of zero cases before a worldwide pandemic was declared by the World Health Organization. Even though there were reports of an increase in infections from all nations, Indonesia did not place travelers under any particular travel restrictions or require them to stay in quarantine while they were there., not even from the worst-affected nations like China (De Salazar PM et al., 2020). On January 27, 2020, 238 Indonesian nationals were evacuated from Wuhan, and travel restrictions were imposed from Hubei province, the COVID-19 global epicenter (AA, 2020).

### *1.2 Explore Importance of the Problem*

When infections started to be reported, Indonesia began to understand how severe the problem was. As a result, it enacted several laws and took other steps to solve COVID-19. One of them is by designating on March 3, 2020, one hundred general hospitals serving as referral hospitals. On March 18, 2020, the number of COVID-19 patients increased; there were 227 Referral Hospitals. But the death toll is rising. (Indonesiabaik.id, 2020). Direct information about COVID-19's effects in Indonesia is available from the Republic of Indonesia's Ministry of Health. Coordinated COVID-19 data is available on the newly launched website. Initially, some mainstream media attacked data openness.

However, the public is increasingly critical and demands that the government provide data transparency. The number of incidents may need to be more reported due to unclear data (Bangkit Indonesiaku, Sehat Negeriku, 2020).

"VUCA" was first established by the US Army War College in 1987. Following the conclusion of the Cold War, unstable geopolitical situations were characterized by volatility, uncertainty, complexity, and ambiguity (USAHEC,2020). This abbreviation is commonly used to describe a chaotic, tumultuous, and quickly evolving corporate environment following the fourth industrial revolution. This method may also be applied in other domains to enhance comprehension of the world and the COVID-19 epidemic. Changes that happen quickly and significantly over a certain length of time are referred to as volatile. A situation or occurrence that is ambiguous is said to be uncertain. The term "complexity" describes the interconnectedness of several essential decision

elements. Being more explicit about the necessary course of action is called ambiguity. We live in a VUCA environment regarding health care (Murugan S et al.,2020).

*1.3 Describe Relevant Scholarship*

The "Ring of Fire," which includes Indonesia, is prone to several natural calamities, including the COVID-19 epidemic. COVID-19 has a comprehensive effect that touches on many facets of life. Hospitals have to run as efficiently as possible during and after a crisis. Hospitals are crucial in delivering health care to afflicted areas by serving as the first line of defense in addressing COVID-19 cases (Mogg R, 2020). Hospital emergency preparedness has long been recognized by the 2015–2030 Sendai Framework for Disaster Risk Reduction (UNDRR, 2015) and the Hyogo Framework for Action, which was developed between 2005 and 2015 and presented at the World Conference on Disaster Reduction 18–22 January 2005 in Kobe, Hyogo, Japan (WCDR, 2005). Both frameworks emphasize the need for efficiency and safety. Because of this pandemic, it is essential to look into and evaluate how prepared Indonesian COVID-19 referral hospitals are to handle the pandemic, which is predicted to last for some time (Firdaus A et al., 2023).

*1.4 State Hypotheses and Their Correspondence to Research Design*

The World Health Organization released a kit for hospitals to prepare for the COVID-19 pandemic, including the COVID-19 Rapid Hospital Preparedness Checklist. This tool may help assess the overall preparedness of hospitals, evaluate healthcare capacity in the case of a COVID-19 pandemic, and suggest specific, essential actions that must be taken before and during the pandemic. Hospitals worldwide can use this product's twelve essential COVID-19 handling components. The 12 component instruments are as follows: human resources, capacity building, clinical patient management, continuity of critical support, leadership and incident management systems, monitoring and information management, coordination and communication risk communication and community engagement, financial administration and business continuity, and health deficiencies, infection prevention control, quick diagnosis, and mental and psychological support. Many nations have used this tool, sometimes known as a checklist. For instance, Lesotho, Nigeria, and Nepal have all employed assessment evaluations. Hospital self-assessments and provincial assessments are being carried out in other nations in the interim. It is also possible to see improvements in the hospitals undergoing evaluation due to deficiencies in the 12 elements of hospital preparedness for COVID-19. Gaps in the COVID-19 Hospital's 12 components Investigations into preparedness may also result in modifications to the assessed hospitals (WHO, 2020).

Based on the background information provided above, this study aims to enhance hospital resilience throughout the recovery phase by capturing the management perspective of Indonesia's Level-2 Army Hospital and Gatot Soebroto Army Central Hospital regarding the COVID-19 pandemic.

## 2. Method

*2.1 Study Design*

This study evaluated hospitals' preparedness for handling the COVID-19 pandemic using a cross-sectional study, which is a quantitative study.

*2.2 Sampling Procedure*

2.2.1 Data Sampling

The study was carried out in Army hospitals located from the provinces of Sumatra to Papua, in the areas under Indonesia's Regional Military Command, from January 2020 to December 2022. Fourteen level-2 army hospitals located throughout several provinces, including the top referral center, Gatot Soebroto Army Central Hospital, served as sites for the research. Participating hospitals were those that gave their consent to take part. All participating hospitals are authorized to participate in this study by the appropriate authorities. The present

investigation employed a non-probabilistic sampling technique per the study's objectives and authorization from each research location.

The location of the Level-2 Army Hospital is in the 1) Regional Military Command I/Bukit Barisan, 2) Regional Military Command II/Sriwijaya, 3) Regional Military Command III/Siliwangi, 4) Regional Military Command IV/Diponegoro, 5) Regional Military Command V/Brawijaya, 6) Regional Military Command VI/Mulawarman, 7) Regional Military Command IX/Udayana, 8) Regional Military Command XII/Tanjungpura, 9) Regional Military Command XIII/Merdeka, 10) Regional Military Command XIV/Hasanuddin, 11) Regional Military Command XVI/Pattimura, 12) Regional Military Command XVII/Cenderawasih, 13) Jayakarta Regional Military Command, 14) Regional Military Command Iskandar Muda, and 15) Gatot Soebroto Army Central Hospital.

2.2.2 Data Collection

Each participating hospital was given a formal letter, a focus group discussion guide, and questions regarding the checklist's implementation and challenges. A total of 15 hospitals consented to participate in the study. Data on hospital aspects, such as the number of beds available, isolation units, intensive care units (ICU), ventilators, and specialist health personnel related to COVID-19, were gathered using a standardized questionnaire. Hospital preparedness data was collected using an updated WHO COVID-19 hospital preparedness checklist (interim version, February 2020). The WHO preparedness checklist was created to help hospitals identify and start the critical steps required to guarantee a quick response to the COVID-19 epidemic. There were 12 main parts to the original checklist, and each part had questions (or indications) about how well the recommended action for that part was being implemented. The research requirements and questionnaire list have been tested previously at the Gatot Soebroto Army Central Hospital because this hospital is the highest referral hospital and is an ideal example for the hospitals below it. Each participating hospital receives a copy of the questionnaire and checklist in soft copy form. One or more hospital representatives who are knowledgeable about hospital service delivery and COVID-19 pandemic preparation, such as the medical director, head of clinical services, and head of the COVID-19 response team, should fill it out.

The evaluation team, including medical professionals, nurses, and representatives from the hospital's technical, administrative, financial, and managerial divisions, collected the data. Professionals with expertise and training in hospital disaster management make up the study's examiners. All assessors agreed on each element's value and level. Assessors already possess the skills and information to determine whether a hospital is prepared for an emergency. Fifteen hospital assessors filled out the COVID-19 Hospital Preparedness Information System form. As stated earlier, this form utilizes the 12 components of the Rapid Hospital Preparedness Checklist for COVID-19, which the World Health Organization created (WHO, 2020) (Table 1). This instrument has twelve major components with several suggested actions (sub-components).

2.3 *Data Analysis*

The evaluation criteria for each component criterion are displayed by data analysis: 1) Not Available: either no plan exists or a plan exists but has not yet begun; 2) Partially Functional: planning is now available but incomplete; or 3) Fully Functional: planning is complete and effective while adhering to relevant criteria.
The analytical method used in this research is a rapid-based checklist of hospital preparedness for COVID-19 to determine the hospital disaster preparedness. The following scoring criteria are used to assign scores to each checklist subcomponent.

$$ComponentScore = \sum SubcomponentScore$$

The Component Score is then divided by the total number of sub-components in each component using the following calculation:

$$Achievementpercentage = \frac{SubscomponentScore}{\sum SubcomponentScore}$$

The hospital's preparedness for managing the COVID-19 pandemic was then assessed using the Achievement Percentage and the WHO assessment system, which is broken down into three categories as shown in table:

Table 1: WHO Scoring classification of hospital preparedness in facing the COVID-19

| Preparedness degree | Percentage fulfilment |
|---|---|
| Not prepared | If the fulfilment value is less than 50% |
| Moderate or Medium preparedness degree | If the fulfilment value is 50-79% |
| Adequate or High preparedness degree | If the fulfilment value is more than 80% |

*2.4. Ethical Considerations*

The ethical clearance number 30/VII/KEPK/2023, which was granted by the ethics committees of Gatot Soebroto Army Central Hospital

**3. Results**

The research results were obtained based on an evaluation of the achievement scores of 15 Army Hospitals using the COVID-19 Hospital Preparedness Information System checklist, which is sourced from the WHO-created Rapid Hospital Preparedness Checklist for COVID-19 (WHO,2020). This instrument has twelve Key Components, each with many Recommended Actions (sub-components).

The research locations were all Level-2 hospitals in the Regional Military Commands area from Sumatra to Papua provinces, with the Gatot Soebroto Central Army Hospital as the highest referral center, Figure 1.

The location of Army hospital are in the 1) Gatot Soebroto Army Central Hospital 2) Iskandar Muda Hospital at Regional Military Command Iskandar Muda 3) Putri Hijau Hospital at Regional Military Command I/Bukit Barisan, 4) AK Gani Hospital at Regional Military Command II/Sriwijaya, 5) Dustira Hospital at Regional Military Command III/Siliwangi, 6) Moh Ridwan Meuraksa Hospital at Jayakarta Regional Military Command, 7) Dr. Soejono Hospital at Regional Military Command IV/Diponegoro, 8) Dr. Soepraoen Hospital at Regional Military Command V/Brawijaya, 9) Dr. R Harjanto Hospital at Regional Military Command VI/Mulawarman, 10) Udayana Hospital at Regional Military Command IX/Udayana, 11) Kartika Husada Hospital at Regional Military Command XII/Tanjungpura, 12) RW Mongisidi Hospital at Regional Military Command XIII/Merdeka, 13) Pelamonia Hospital at Regional Military Command XIV/Hasanuddin, 14) Prof Dr JA Latumeten Hospital at Regional Military Command XVI/Pattimura, 15) Marthen Indey Hospital at Regional Military Command XVII/Cenderawasih.


Figure 1: The location of the Regional of Military Commands where thelevel 2 hospital were studied.

The distribution of the locations of level 2 army hospitals in Indonesia is depicted in Figure *2*.


Figure 2: Map of Indonesia and fifteen hospitals that took part in theresearch, spread across each province.

The VUCA conditions faced by various hospitals in Indonesia, considering the uncertain nature of the COVID-19 pandemic, mean that the Indonesian Army must play a big role in providing health services because its presence is distributed throughout military regional command areas.

3.1 *Hospital Preparedness of the Gatot Soebroto Army Central Hospital*

Gatot Soebroto Army Central Hospital, as the highest reference and main reference point for the Presidency, must be ready to fight COVID-19 because there were still many unknown things at the beginning of the pandemic. At that time, no one was immune to COVID-19, the emergence of various hoaxes resulted in obstacles in handling it, there was no appropriate medicine, and no country was ready to face a pandemic. The number of cases of infection in various countries increased, and it seemed as if the country had no national borders. There were many questions about whether this was a natural or artificial manufactured infection.

Outpatient and inpatient COVID-19 patients at RSPAD numbered 39,981 people from the beginning of 2020 to 2023. Inpatients have severity levels, namely patients without symptoms (asymptomatic), mild, moderate, and severe. Of all patients, 81 % are inpatients with moderate to severe symptoms. The death rate for inpatients during the three years at RSPAD was 1,051. Preparedness for handling COVID-19 is essential.

The legal standing of RSPAD Gatot Soebroto is based on several regulations: 1) Army Chief of Staff Regulation No. 26 of 2019 concerning the Organization and Duties of RSPAD GS is to support the main tasks of the Army and Armed Forces. 2) Regulation of the Commander of the Armed Forces No. 45 of 2017 concerning RSPAD GS as the Highest Reference for Armed Forces. 3) Presidential Decree no. 18 of 2018 concerning RSPAD as the Main Reference for the Presidency and becoming the Icon Presidential Hospital. 4) Minister of Health Decree Number 169 of 2020 concerning the designation of Referral Hospitals for Handling Certain Emerging Infectious Diseases, and 5) Minister of Finance Decree Number 804/KMK.05/2016 dated November 8, 2016, concerning the designation of RSPAD Gatot Soebroto as a Government Agency that implements the Financial Management Pattern for Public Service Bodies (PPK-BLU).

In carrying out the first key component of the 12 preparedness checklists from WHO, the leadership and incident management system, Gatot Soebroto Army Central Hospital seeks to implement seven recommended actions:

a) Forming an emergency disease management team.
b) Conducting pandemic simulation rehearsals.
c) Establishing various standard operating procedures during a pandemic.
d) Creating a COVID-19 countermeasures post that gives morning reports every day,
e) Carrying out tabletop exercises,
f) Making a hospital disaster plan, and
g) Centralize the treatment room for COVID-19 patients

In implementing the second key component, namely communication and coordination from WHO, internally, Gatot Soebroto Army Central Hospital activated communication and expanded communication tools (mobile phones, WhatsApp, email, and call centers) for all staff, patients, and visitors. Externally, it carried out dissemination and re-education about emergency infectious diseases to various media, training COVID-19 spokespersons, and communicating every day in forums with the supra system (Army Headquarters, Armed Forces Headquarters, Ministry of Health, etc.), reporting daily data and embracing philanthropists and donors to participate in overcoming Covid-19.

Following the recommendation of the third key component, Army Central Hospital will prepare protocols and Standard Operating Procedures (SOP) that are accessible to all employees, patients, visitors, and the general public to understand more about the communication risk regarding infection prevention and control. The hospital has designated personnel to gather, examine, and distribute information on COVID-19 and its services, adhering to the necessary protocols.

Outpatient and inpatient COVID-19 patients at Army Central Hospital numbered 39,981 people from the beginning of 2020 to 2023. Inpatients have severity levels, namely patients without symptoms (asymptomatic), mild, moderate, and severe. Of all patients, 81 % are inpatients with moderate to severe symptoms. The death rate for inpatients during the three years at Army Central Hospital was 1,051. Preparedness for handling COVID-19 is essential.

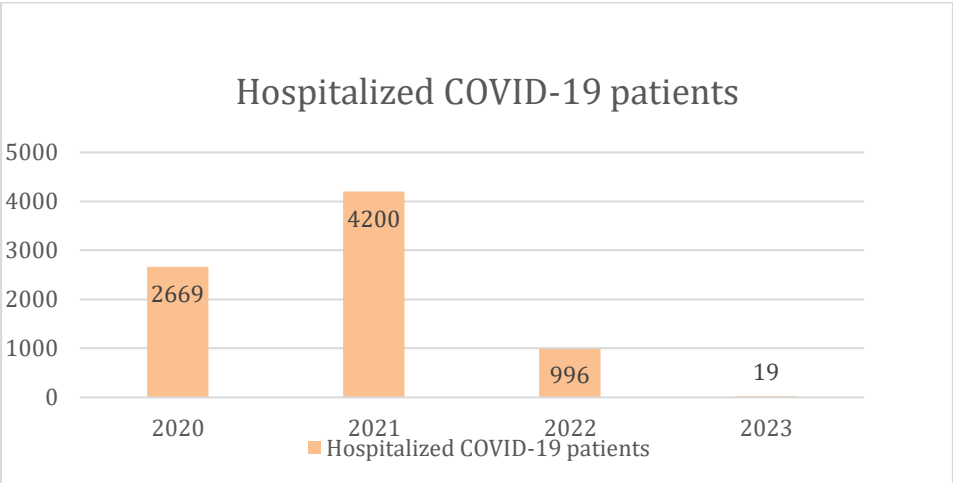



Figure 3: Number of hospitalized COVID-19 patients.

Figure 3 shows the data on COVID-19 patients in Inpatient and Emergency Care Patients. The number of COVID-19 patients in 2020 was 2,669; then, in 2021, there were cases, namely 4,200 patients. In the following year, 2022, Covid-19 patients decreased to 996 and 19 patients. The highest number of cases of hospitalized patients occurred in 2021 (4200).

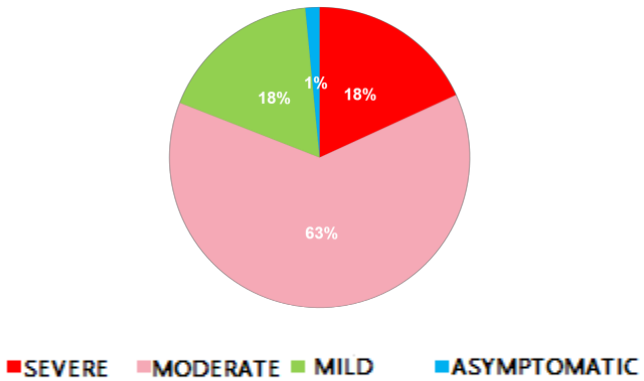



Figure 4: Diagrams of severity level COVID-19 hospitalized patients

In general, 63% of inpatients treated in Gatot Soebroto Army Central hospital had a moderate severity level of condition.

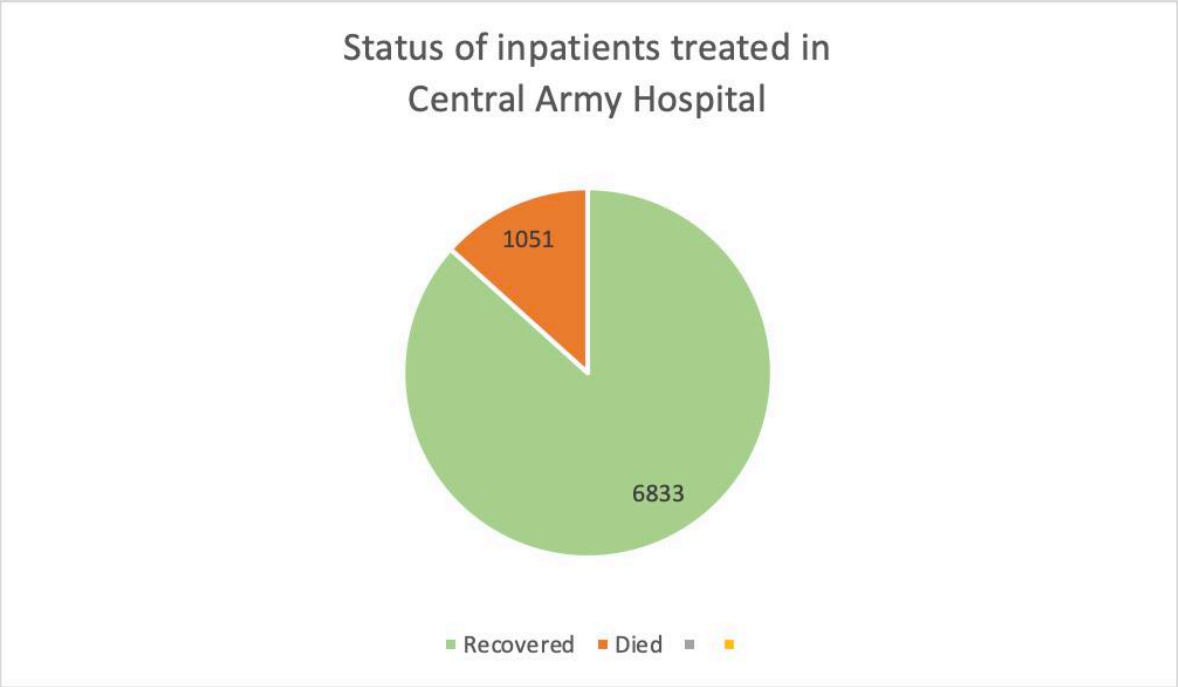



Figure 5: The status of s treated in Army Central Hospital

Case Fatality Rate was 13.3%, occurring in patients with severe level (18%).

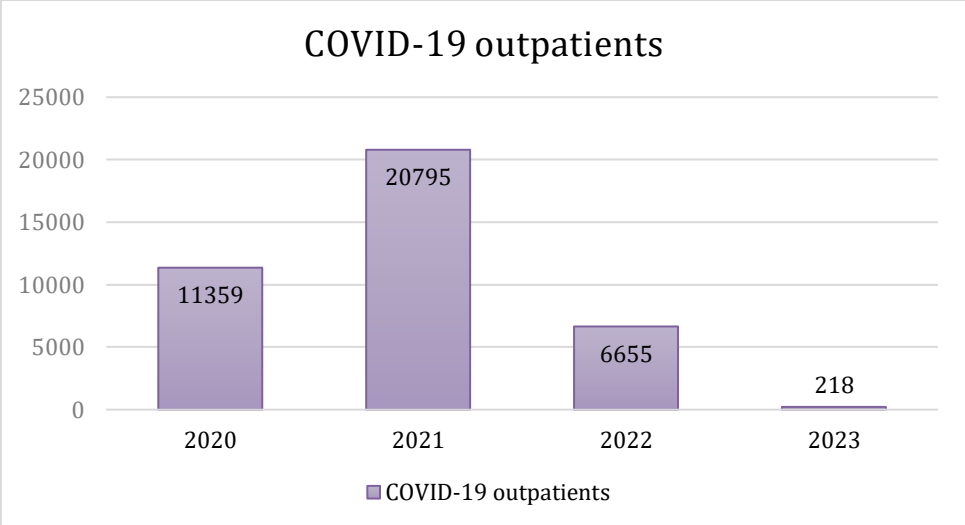



Figure 6: COVID-19 outpatients. The highest outpatient visits occurred in 2021 (20,795).

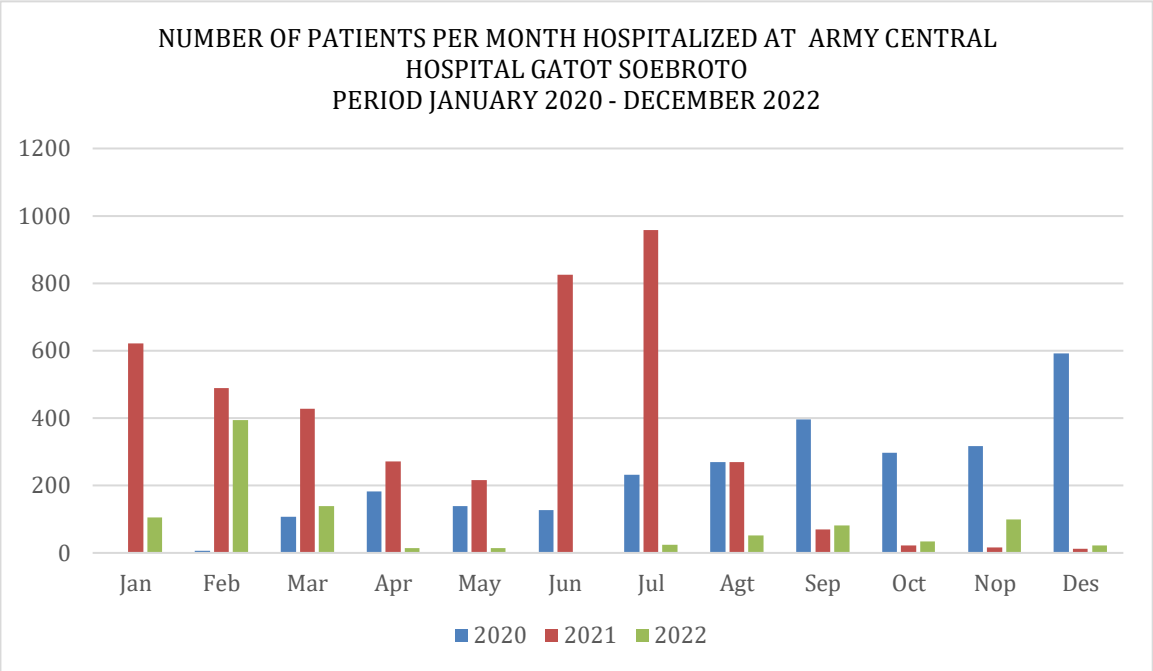



Figure 7: Number of patients per month hospitalized at Army Central Hospital period January 2020 – December 2022. The peak incidence of COVID- 19 occurred in July 2021.

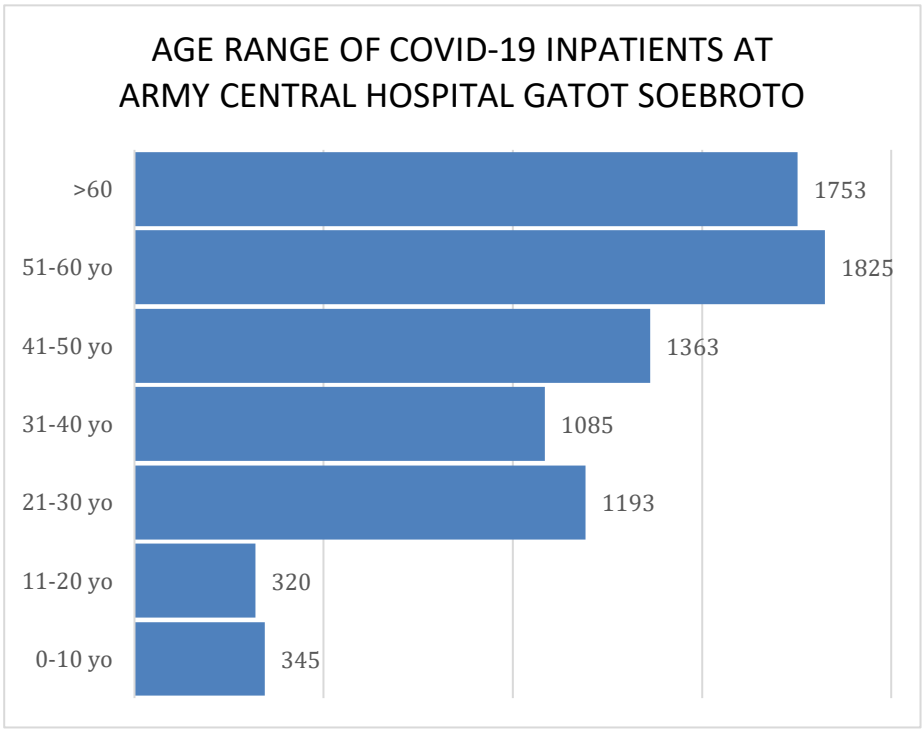



Figure 8: Age range of COVID-19 inpatients at Army Central Hospital

The fourth key components are risk communication and community engagement. Army Central Hospital built a policy of "four healthy, five perfect" (1. Wear a mask and scan body temperature; 2. Hand hygiene and a clean and healthy lifestyle, 3. Physical restrictions, 4. Tools self-protection, 5. Comply with policies according to SOP, Clinical Pathway, and Speak Up Culture). They set up a COVID-19 Call Center and Information Corner, a COVID-19 educational video, an abolition of visiting hours, and a waiting policy with antigen swabs.

The fifth component is financial administration and business continuity. Even WHO suggested that all purchasing, supplying, and required services for COVID-19 management. Army Central Hospital made a system for procuring health equipment and health supplies according to priority scale. The Ministry of Health directly guarantees the management of COVID-19 patients by diverting the state budget. Because Army Central Hospital is a COVID-19 treatment center, medical personnel recruitment from various other health facilities is accompanied by a temporary practice permit. When the escalation of COVID-19 increases, there are restrictions on services for non-COVID-19 patients.

The sixth component is Human Resources, Army Central Hospital updated internal rotation, recruitment of volunteers, organization of education and training and research and development, periodic medical health examination, vaccination, and facilitation of Work from Home for High-Risk Human Resources.

The seventh component is surge capacity. Army Central Hospital developed emergency installations, central surgery installations, hemodialysis capacities, inpatient rooms, and laboratory facilities.

The eighth is continuity of essential service support. Army Central Hospital developed the report system for daily, weekly, and monthly evaluations among the team and hospital leaders through video conferences with the supra system. The top on-duty officers, as representatives of the hospital director, make decisions regarding COVID-19 services.

The ninth component is the clinical management of patients. Army Central Hospital builds daily integrated reports using the satellite method, Telemedicine and VIP patient home visits, Commander hours of distancing, Use of HT for communication between officers in the treatment room, Use of CCTV for patient monitoring, Support from Minister of Defense / Indonesian Army Commander / Head of force units land by building a field hospital TNI/Head of force units land by building a field hospital and We are facing the escalation of COVID-19 patients. The ten components are occupational health, mental health, and psychosocial support. All hospital staff are protected, trained, and equipped with Personal Protective Equipment (PPE) to provide medical services to all patients. The Director supports additional incentives, logistics / extra food, accommodation for health workers, psychosocial and mental health support available for hospital staff, family, and patients, online entertainment, insurance, reward systems, and others.

The eleventh component is rapid identification and diagnosis of COVID-19, including the development of a rapid PCR laboratory, namely the second Army Central Hospital PCR laboratory that is recognized after the Ministry of Health; developed online COVID-19 screening, one-stop COVID-19 outpatient service, drive-thru swab PCR, and home visit PCR swabs. All laboratories and reception areas are equipped with information and posters regarding Personal Protective Equipment (PPE) and biosafety to handle samples, including their disposal safely.
The twelfth component is infection prevention and control. Army Central Hospital is working on COVID-19 service protocols, using PPE according to zoning, outreach, re-education on disease prevention and control, and creating standards for isolation rooms. To prevent transmission, including airborne transmission, create patient service facilities, provide hand hygiene facilities, limit visitors, and maintain distance. Maintain cleanliness and sanitation of the environment and equipment. Manage the bodies of COVID-19 patients.

### 3.2 *Hospital Preparedness of the Level-2 Army Hospital in Indonesia*

There are 14 Level-2 hospitals within the Indonesian Army, all of which are classified as type B. All of the data are as follows on the information system dashboard after respondents have completed the COVID-19 Hospital Preparedness information system form:

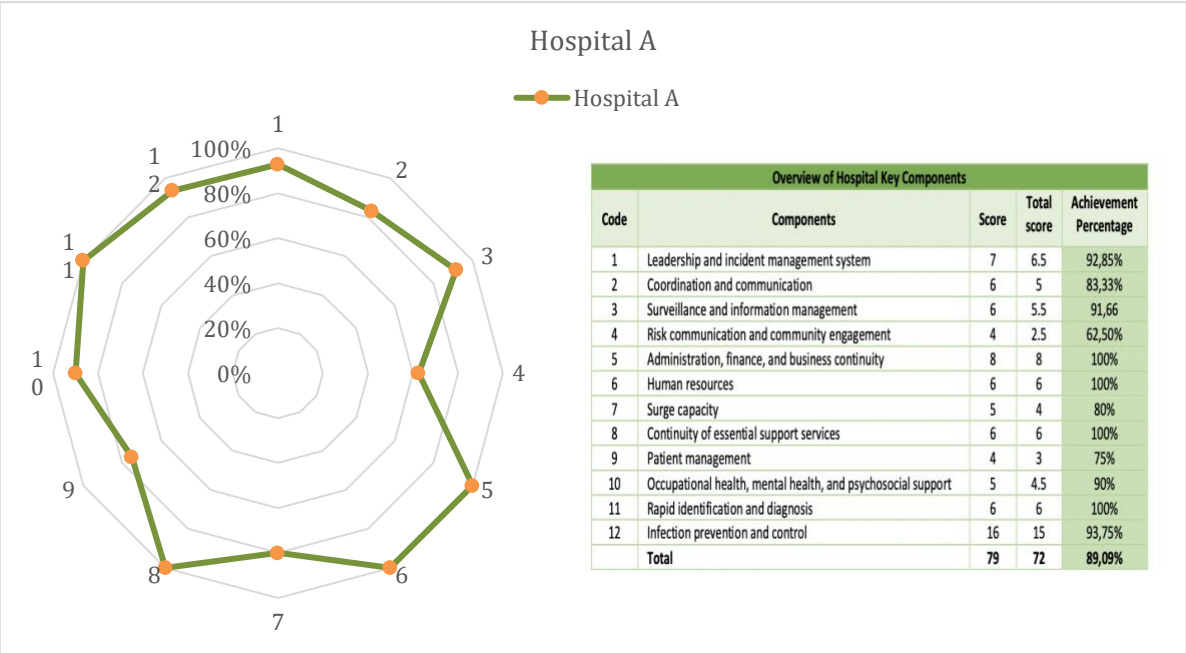
Table 3: Achievement percentage of COVID-19 hospital preparedness at 15 Army hospitals from Sumatera to Papua. (Hospital H and Hospital I); and North Sumatra (Hospital J and Hospital K).

| **Hospital Achievement Percentage** | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Code** | **Components** | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** | **I** | **J** | **K** | **L** | **M** | **N** | **O** |
| 1 | Leadership and incident management system | 92,8% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 50% | 100% | 100% |
| 2 | Coordination and communication | 83,3% | 83,3% | 83,3% | 100% | 100% | 100% | 100% | 83,3% | 100% | 75% | 100% | 100% | 50% | 100% | 100% |
| 3 | Surveillance and information management | 91,6% | 83,3% | 83,3% | 91,6% | 100% | 100% | 100% | 91,6% | 83,33% | 66,6% | 100% | 100% | 50% | 100% | 100% |
| 4 | Risk communication and community engagement | 62,5% | 100% | 100% | 100% | 100% | 100% | 100% | 62,5% | 100% | 100% | 100% | 100% | 50% | 100% | 100% |
| 5 | Administration, finance, and business continuity | 100% | 81,2% | 93,7% | 87,5% | 100% | 100% | 100% | 87,5% | 100% | 100% | 100% | 100% | 31,2% | 100% | 100% |
| 6 | Human resources | 100% | 75% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 41,6% | 100% | 100% |
| 7 | Surge capacity | 80% | 80% | 80% | 80% | 80% | 100% | 100% | 60% | 100% | 100% | 100% | 100% | 10% | 100% | 100% |
| 8 | Continuity of essential support services | 100% | 100% | 91,6% | 100% | 100% | 100% | 100% | 83,3% | 100% | 100% | 100% | 100% | 58,3% | 100% | 100% |
| 9 | Patient management | 75% | 87,5% | 100% | 100% | 75% | 100% | 100% | 87,5% | 75% | 75% | 87,50% | 100% | 37,5% | 100% | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 90% | 40% | 100% | 70% | 100% | 100% | 100% | 100% | 80% | 90% | 100% | 100% | 30% | 100% | 100% |
| 11 | Rapid identification and diagnosis | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| 12 | Infection prevention and control | 93,7% | 90,6% | 100% | 96,8% | 100% | 100% | 100% | 93,7% | 100% | 100% | 100% | 100% | 96,8% | 100% | 100% |
| | **Total** | **89,1%** | **78,1%** | **94,3%** | **93,8%** | **97,9%** | **100%** | **100%** | **80,1%** | **94,8%** | **92,2%** | **98,95%** | **100%** | **50,4%** | **100%** | **100%** |

Table 3 displays the number of hospitals that meet the requirements and the list of 15 Army hospitals that have completed the form for the Not Ready (≤ 50%), Moderate or Moderate Preparedness degree (50-79%), and Sufficient or High Preparedness degree (≥ 80%) categories. From this table, Radar Graph was created which reflects the hospital's preparedness achievements in facing the pandemic. There are 5 hospitals that can carry out the WHO Hospital Preparedness checklist >80% with a score of 100%, there are achievements above 80% but below 100% in 8 hospitals, while the achievement was below 80% there were 2 hospitals.

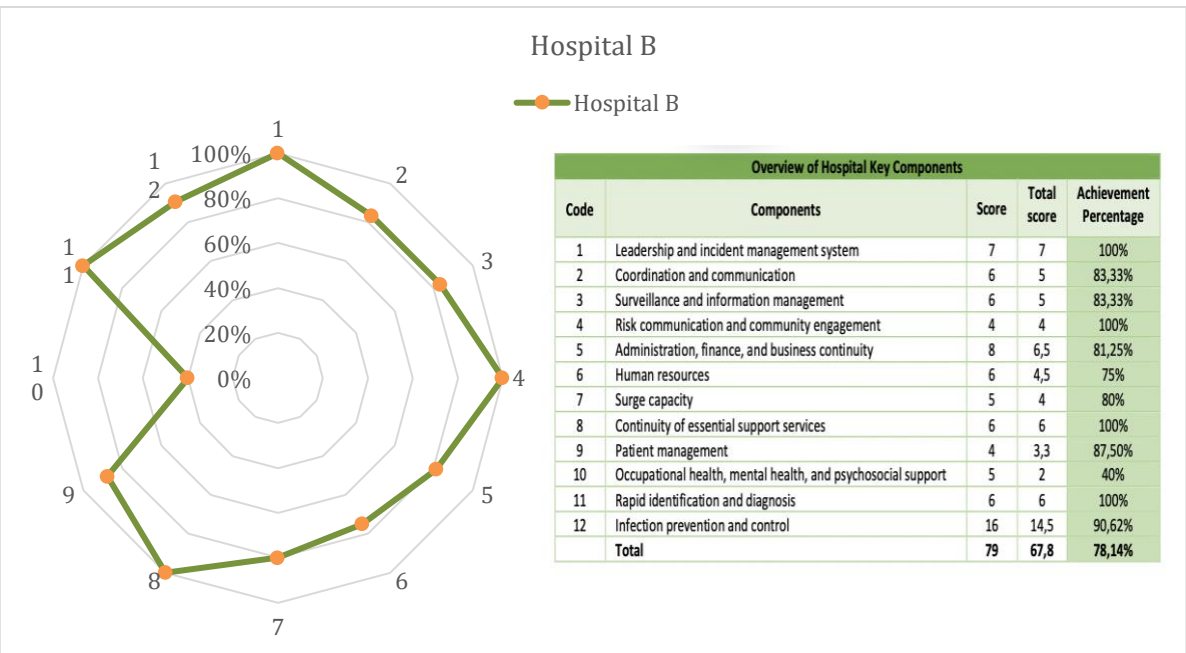
The achievement of hospital preparedness for each hospital that we randomly display is as follows:

1. Hospital A



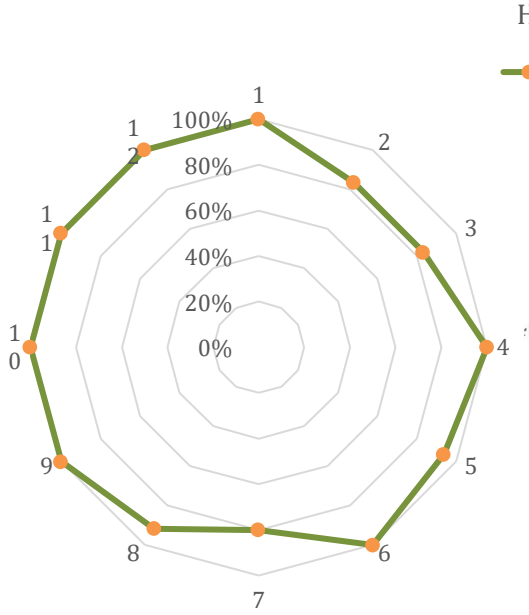

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 6.5 | 92,85% |
| 2 | Coordination and communication | 6 | 5 | 83,33% |
| 3 | Surveillance and information management | 6 | 5.5 | 91,66 |
| 4 | Risk communication and community engagement | 4 | 2.5 | 62,50% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 4 | 80% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 3 | 75% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 4.5 | 90% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 15 | 93,75% |
| | **Total** | **79** | **72** | **89,09%** |

2. Hospital B



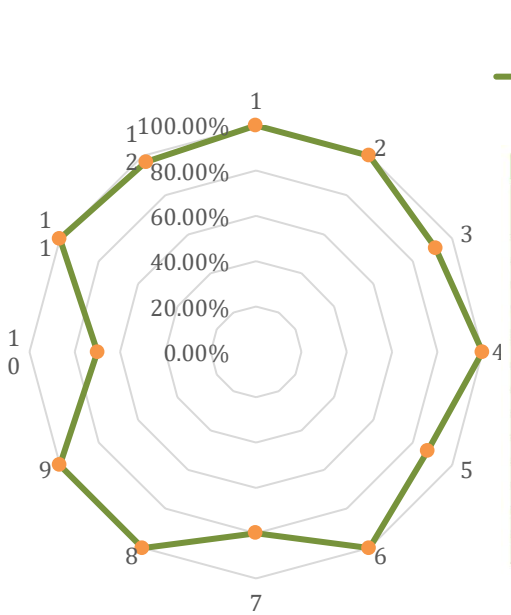

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 5 | 83,33% |
| 3 | Surveillance and information management | 6 | 5 | 83,33% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 6,5 | 81,25% |
| 6 | Human resources | 6 | 4,5 | 75% |
| 7 | Surge capacity | 5 | 4 | 80% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 3,3 | 87,50% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 2 | 40% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 14,5 | 90,62% |
| | **Total** | **79** | **67,8** | **78,14%** |

3. Hospital C



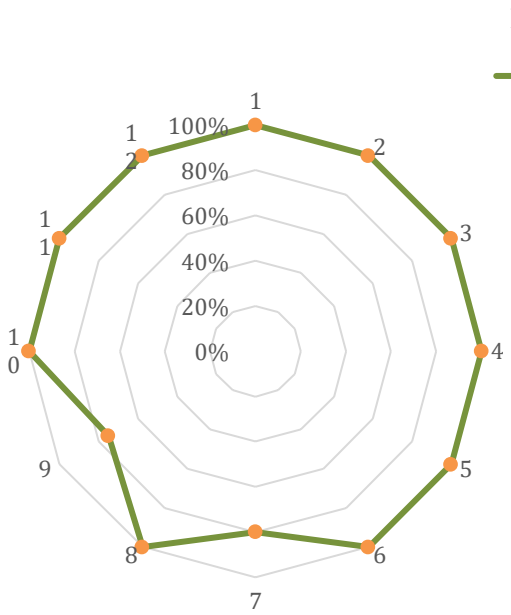

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 83,33% |
| 3 | Surveillance and information management | 6 | 6 | 83,33% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 7,5 | 93,75% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 4 | 80% |
| 8 | Continuity of essential support services | 6 | 5,5 | 91,66% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **77** | **94,33%** |

4. Hospital D



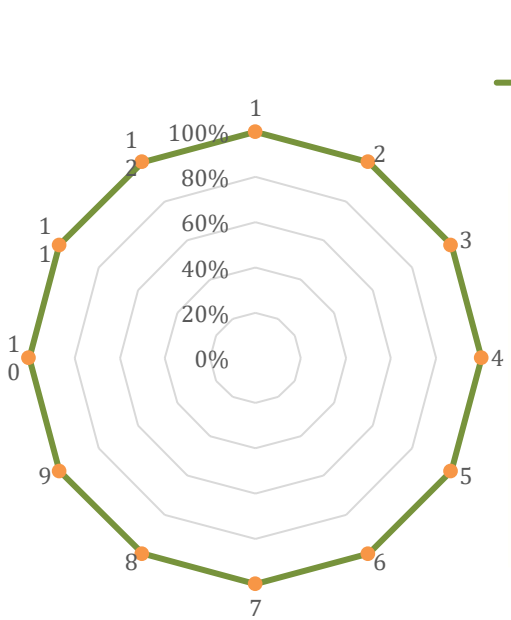

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 5,5 | 91,66% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 7 | 87,50% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 4 | 80% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 3,5 | 70% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 15,5 | 96,87% |
| | **Total** | **79** | **74,5** | **93,83%** |

5. Hospital E



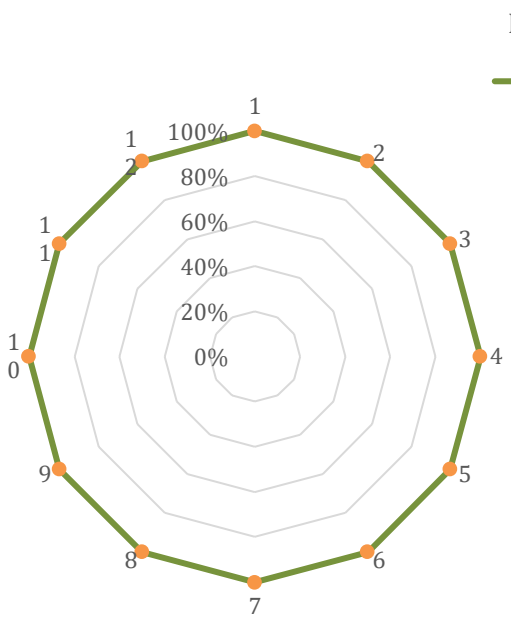

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | S chart and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 3,5 | 80% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 3 | 75% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **76,5** | **97,91%** |

6. Hospital F



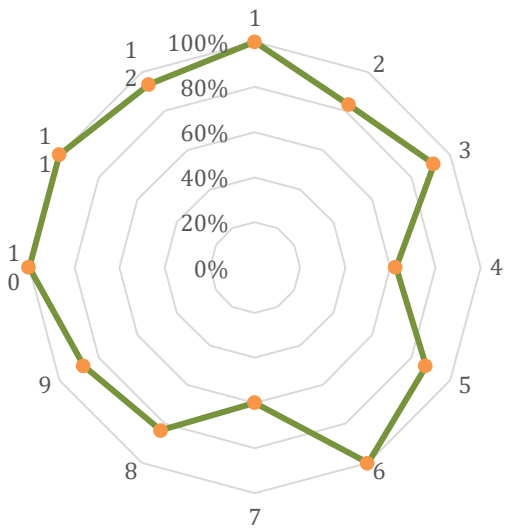

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **79** | **100%** |

7. Hospital G



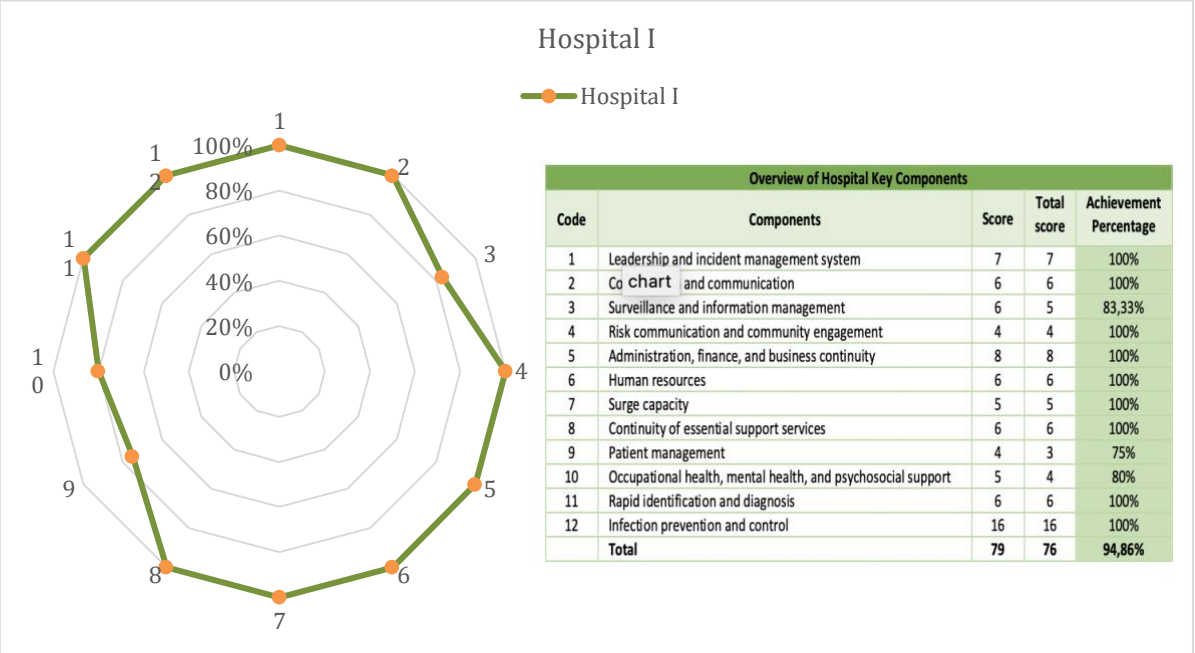

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **79** | **100%** |

8. Hospital H



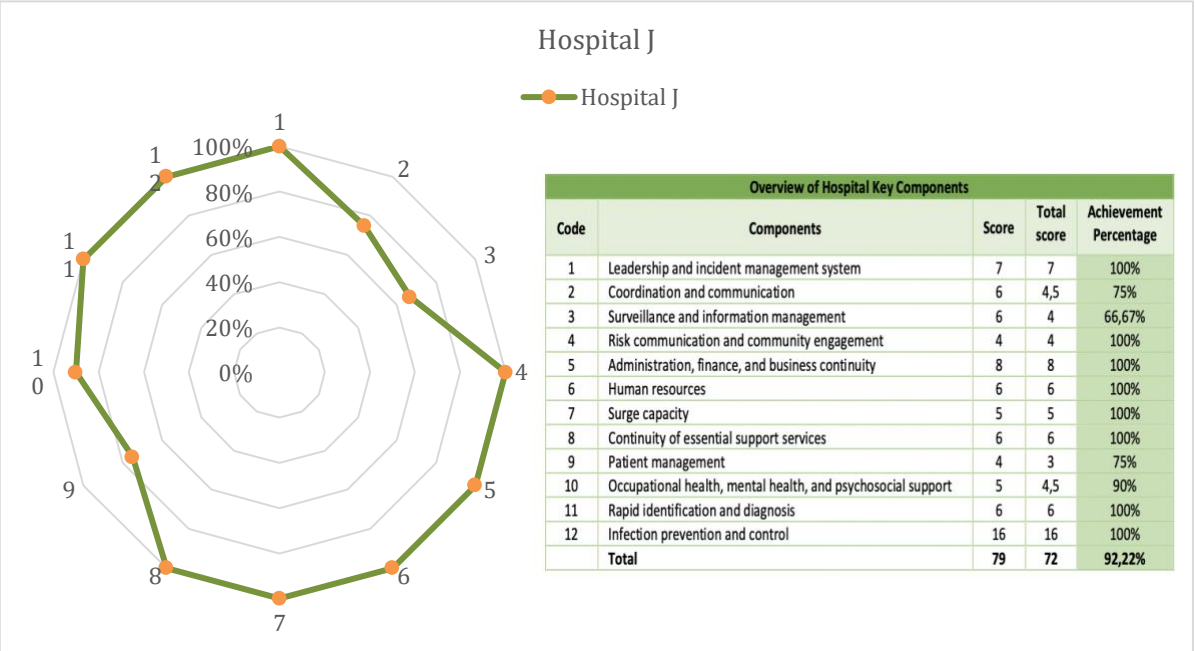

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 6 | 100% |
| 2 | Coordination and communication | 6 | 5 | 83,33% |
| 3 | Surveillance and information management | 6 | 5,5 | 91,66% |
| 4 | Risk communication and community engagement | 4 | 2,5 | 62,50% |
| 5 | Administration, finance, and business continuity | 8 | 7 | 87,50% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 3 | 60% |
| 8 | Continuity of essential support services | 6 | 5 | 83,33% |
| 9 | Patient management | 4 | 3,5 | 87,50% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 15 | 93,75% |
| | **Total** | **79** | **69,5** | **80,17%** |

9. Hospital I



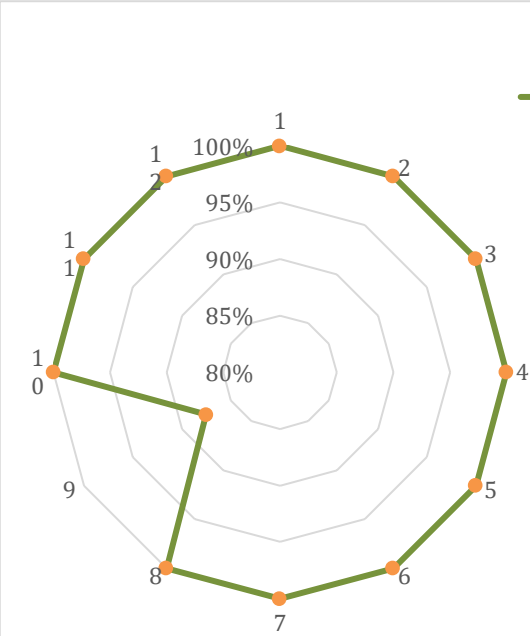

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 5 | 83,33% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 3 | 75% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 4 | 80% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **76** | **94,86%** |

10. Hospital J



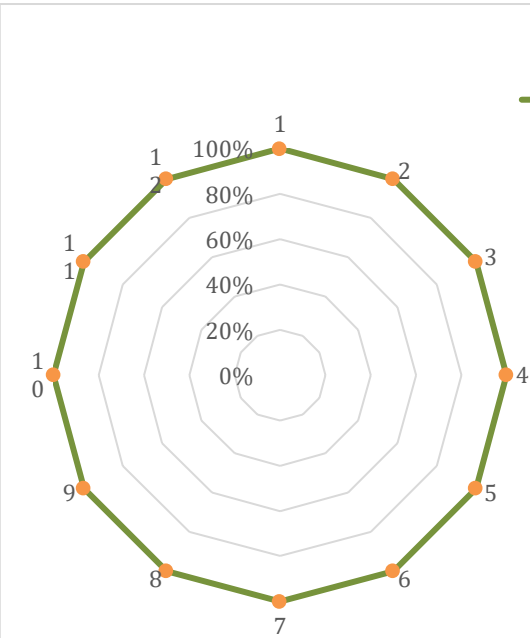

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 4,5 | 75% |
| 3 | Surveillance and information management | 6 | 4 | 66,67% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 3 | 75% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 4,5 | 90% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **72** | **92,22%** |

11. Hospital K



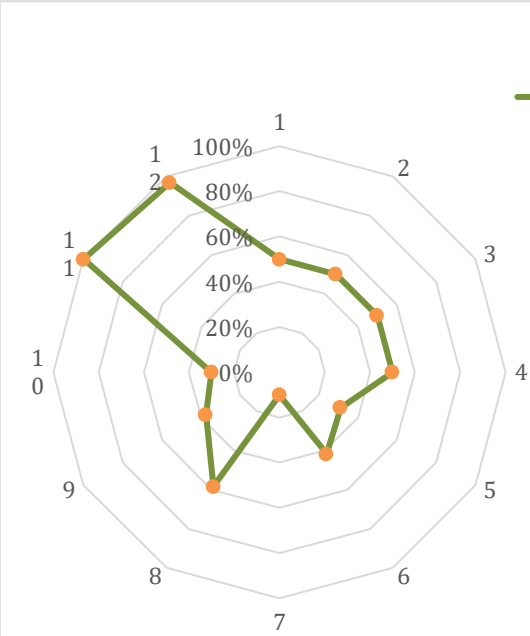

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 3,5 | 87,50% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **78,5** | **98,95%** |

12. Hospital L



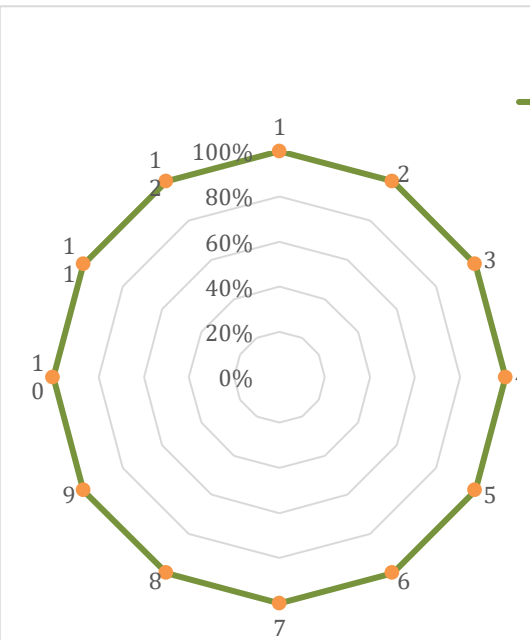

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **79** | **100%** |

13. Hospital M



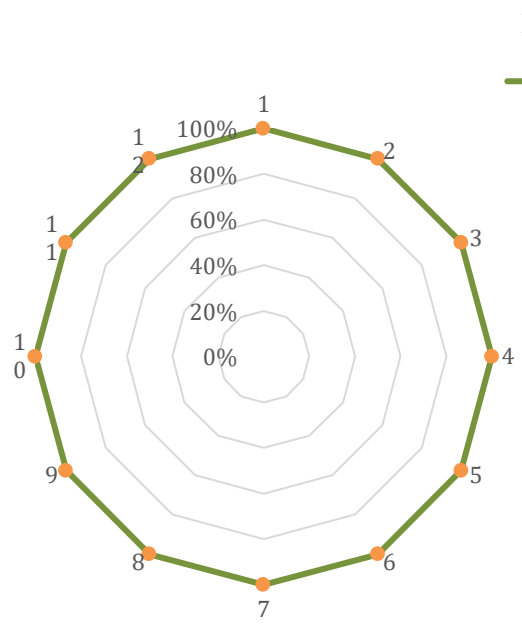

| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 3,5 | 50% |
| 2 | Coordination and communication | 6 | 3 | 50% |
| 3 | Surveillance and information management | 6 | 3 | 50% |
| 4 | Risk communication and community engagement | 4 | 2 | 50% |
| 5 | Administration, finance, and business continuity | 8 | 2,5 | 31,25% |
| 6 | Human resources | 6 | 2,5 | 41,66% |
| 7 | Surge capacity | 5 | 0,5 | 10% |
| 8 | Continuity of essential support services | 6 | 3,5 | 58,33% |
| 9 | Patient management | 4 | 1,5 | 37,50% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 1,5 | 30% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 15,5 | 96,87% |
| | **Total** | **79** | **45** | **50,46%** |

14. Hospital N




| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **79** | **100%** |

15. Hospital O




| Overview of Hospital Key Components | | | | |
|---|---|---|---|---|
| Code | Components | Score | Total score | Achievement Percentage |
| 1 | Leadership and incident management system | 7 | 7 | 100% |
| 2 | Coordination and communication | 6 | 6 | 100% |
| 3 | Surveillance and information management | 6 | 6 | 100% |
| 4 | Risk communication and community engagement | 4 | 4 | 100% |
| 5 | Administration, finance, and business continuity | 8 | 8 | 100% |
| 6 | Human resources | 6 | 6 | 100% |
| 7 | Surge capacity | 5 | 5 | 100% |
| 8 | Continuity of essential support services | 6 | 6 | 100% |
| 9 | Patient management | 4 | 4 | 100% |
| 10 | Occupational health, mental health, and psychosocial support | 5 | 5 | 100% |
| 11 | Rapid identification and diagnosis | 6 | 6 | 100% |
| 12 | Infection prevention and control | 16 | 16 | 100% |
| | **Total** | **79** | **79** | **100%** |

## 4. Discussion

*4.1 Previous history of research on hospital preparedness in facing the COVID-19 pandemic*

A questionnaire created by the WHO Regional Office for the Eastern Mediterranean Region was utilized in previous research carried out in pediatric and adult ICUs at Cairo University and 22 Eastern Mediterranean Region (Labib et al., 2020). Its ten main components are as follows: quick identification, diagnosis, isolation and case management, information, communication, human resources, operational support, logistics and supply management, increased capacity and continuity of critical services, and infection prevention and control (WHO EURO, 2020). These studies show hospitals were only moderately prepared when the COVID-19 pandemic started (Ravaghi et al., 2022).

Comprehensive Hospitals are also used in other investigations. The COVID-19 checklist for preparation was released by the US Centers for Disease Control and Prevention (CDC) (Qarawi ATA et al., 2021). This checklist includes information on making decisions and creating plans, developing written COVID-19 plans, and the entire COVID-19 plan, which includes things like facility communications, durable and consumable medical supplies and equipment, managing sick patients, accessing and moving around facilities, occupational health, education and training, and health services/capacity spike) (Qarawi ATA et al., 2021). By applying this checklist, Qarawi et al. concluded that hospitals must be more prepared to handle COVID-19 services (CDC, 2021).

Initially developed by the WHO regional office for Europe and used in earlier studies conducted in Nigeria, the Hospital Preparedness Checklist for COVID-19 was expanded to include the availability of essential resources and the safety of the staff. There were 13 components and 124 indicators in the modified checklist. After pre-testing the study checklist and questionnaire, one of the COVID-19 treatment centers was removed from the survey. According to the study, most participating Nigerian hospitals were equipped to handle the COVID-19 pandemic (Ogoina D et al., 2021).

The World Health Organization Pan American checklist (PAHO 2019) was standardized and used in another prior study conducted in Mazandaran Province, Iran (PAHO, 2019). The ten components that comprise this checklist are the incident management system, coordination, information management, logistics, finance and administration, detection, diagnosis, isolation, case management, and infection prevention and control. The hospital can manage

the COVID-19 pandemic outbreak since it is well-prepared. Superior quality Hospitals in the province of Mazandaran were well-prepared for the COVID-19 pandemic. However, due to the length of the pandemic and the unpredictability of its end, it is imperative to monitor the critical components to maintain a high degree of preparedness (Hosseini SH et al., 2021).

Data for the study were gathered in Indonesia through focus group talks led by Dhamanti et al. Nine organizations from East Java and Bali provinces participated in the study, which was carried out in October 2021 in East Java, Indonesia. The Data's thematic analysis findings were presented using a narrative format. Participating hospitals must practice filling out a hospital preparedness checklist every three months. The participating hospital faces several difficulties, including manually entering data into the checklist, lack of coordination and communication, and different opinions about the lack of a technical guide, feedback, and the data returning empty due to filling errors. This study, which included hospitals and the health office, detailed the difficulties in determining the program's efficacy. Hospitals and the District Health Office had specific issues with the present system (Dhamanti I et al.,2022).

The World Health Organization's rapid hospital preparedness checklist for COVID-19, which consists of 12 components, was used in a cross-sectional study conducted in Indonesia from March to September 2022 to assess hospital preparedness. During the initial year of the COVID-19 pandemic, the research was conducted on the islands of Sumatra, Kalimantan, Java, Bali-Nusa Tenggara, Maluku, and Papua. According to the findings, hospitals in Yogyakarta's Special Region and Jakarta's Capital Special Region have appropriate levels (≥ 80%). In the meantime, hospitals in North Sumatra and West Java range in preparedness from 50% to 79%, adequate (≥ 80%), and moderate (50 - 79%) to not ready (≤ 50%). According to the findings, only 46% of health services routinely evaluate their COVID-19 operational strategies. The assessment results also show that, in comparison to the other two provinces (West Java and North Sumatra), the hospital preparedness in the Central Special Region of Jakarta and the Special Region of Yogyakarta is generally better in the following areas: administration, finance, and business continuity; human resources; surge capacity; continuity of critical support services; and patient management. Even though practically all hospitals have COVID-19 preparedness guidelines for the pandemic, evaluations of the implementation of these policies or preparedness simulations have not been carried out (Lestari et al., 2023).

*4.2 Hospital preparedness in facing the COVID-19 pandemic at Army Central Hospital and Army Hospital Level-2*

In implementing 12 hospital preparedness indicators, Army Central Hospital experienced several obstacles due to the spike in COVID-19 cases, which required a lot of isolation in inpatient rooms. For this reason, several inpatient rooms have been used as isolation rooms for COVID-19 patients and a field hospital in the vehicle parking lot.

Based on data on the age range of patients infected with COVID-19, they are generally adults, and most are in the 51-60 year age range, so medical personnel in this age group are advised to work from home. This results in a reduction in medical personnel. The shortage of medical personnel to provide services for COVID-19 cases is supplemented by deploying medical personnel from Army hospitals levels-3 and level-4 and non-medical personnel from regional military command. The still-uncertain management of COVID-19 led to the development of various therapeutic procedures, resulting in the demand for multiple types of non-standardized drugs growing considerably.

During the COVID-19 pandemic, Army Central Hospital documented all activities, including conducting various research on managing COVID-19. Gatot Soebroto Hospital even received an award as the first hospital to conduct convalescent plasma research and the hospital with the most complete documentation of COVID-19.

In addition to carrying out the WHO hospital preparedness checklist, Army Central Hospital also carried out outreach on COVID-19 vaccination. At first, COVID-19 vaccination was very difficult to implement because there were still many pros and cons, but continuous outreach can increase the coverage of people who receive the COVID-19 vaccine. To eliminate doubts in the community regarding the safety of the COVID-19 vaccine, Army

Central Hospital Gatot Soebroto initiated a kick of vaccine, which must first be given to the President of the Republic of Indonesia, Joko Widodo, and disseminated to the entire community. The vaccination program was followed by the COVID-19 vaccination activity, which army hospitals throughout Indonesia spearheaded, followed by all health institutions and the wider community to achieve the herd immunity target in administering the vaccine.

Regional hospitals are overwhelmed by the surge in patients infected with the coronavirus. The difficulties experienced are mainly related to management and infrastructure in providing services. COVID-19 is a deadly infectious disease in a short time. Patients who experience acute respiratory system failure require special facilities and infrastructure such as ICU, special isolation rooms, oxygen, or ventilators, while these facilities are minimal. In implementing the WHO hospital preparedness checklist, various obstacles depend on the condition of each hospital. Two Army hospitals are at a medium preparedness level (50% - 79%), while 13 other hospitals are at a high preparedness level > 80%. The Army Headquarters focuses on supporting facilities and human resources for various army hospitals.

The key component, patient management, has the highest difficulty level. The obstacles in this case are the availability of space for patient care and medicines that must be prepared and the inadequate availability of medical equipment, including ventilators and intensive care rooms.

The information from the COVID-19 Task Force projects that the need for ventilators to treat the coronavirus in Indonesia will reach around 29.9 thousand units. However, the availability of this tool was only 8.4 thousand units as of March 2020. Only four provinces have more than half the ventilator requirements in their region, namely North Kalimantan (72.7%), Bangka Belitung (69.8%), DKI Jakarta (55.9%), and West Sulawesi (51.6%). Meanwhile, availability in other provinces is 20-30% (Databooks, 2020).

The data obtained in this study show that five army hospitals could not achieve 100% of achievement percentage categories on this key component; four hospitals got a score of 75%, and one hospital got a score of 37.5%. One hospital is in the Sulawesi region, one is in Sumatra, two are on the island of Java, and one is in the Maluku region. Another difficulty level is in key component 10: occupational health, mental health, and psychosocial support. Personal Protective Equipment (PPE) is available to provide medical services to COVID-19 patients. Medical supervision of hospital staff, suspected cases in their families, and close contacts because hospital staff serving COVID-19 tend to create stigma. Medical staff must be provided psychosocial and mental health support, including providing more significant incentives. Some hospitals cannot meet the achievement percentage of 100%: one hospital in Sumatra (40%), one in Kalimantan (70%), and one in Maluku province (30%). Hospitals generally face a shortage of PPE for medical staff and cannot provide appropriate incentives due to hospital services being disrupted by this pandemic. The Ministry of Health provides support through incentives for medical officers who provide COVID-19 services based on workload. In the Sumatra, Kalimantan, and Maluku regions, the number of cases is smaller than in the Java island region, so the incentives differ from those who face the burden due to the large number of cases.

The workload faced by nurses in hospitals during the COVID-19 pandemic is that the number of patients is increasing all the time, the workload carried out is uneven, there is concern about exposure to the virus, and there is very little rest time (Bruyneela A et al., 2021). When COVID-19 first appeared, nurses were overworked and under a lot of stress since they had to utilize personal protective equipment (PPE) in their work schedules; they had little downtime and didn't consume any food or drink before the end of the designated working hours at that point. (Siagian E, et al.,2022). The 14-day isolation of nurses who cared for COVID-19 patients precluded them from engaging in their usual social activities, leading to their social distancing from friends, family, and neighbors. Many believe that nurses who care for patients with COVID-19 will also receive a diagnosis (Siagian E et al.,2022).

Another obstacle is the 4th key component: Risk communication and community engagement. Some areas found difficulties in communication channels between hospital staff and referral hospitals. Three hospitals cannot

achieve an Achievement percentage of 100%, namely one hospital in Kalimantan (40%), one hospital in Sumatra (70%), and one hospital in Maluku (30%).

In today's information age, both too much and too little knowledge might be disastrous. Despite facing the same threats, local communities have experienced different impacts during this pandemic. This report further states that risk communication that is not well planned tends to create new risks and disrupt disaster management efforts (Khan S et al., 2020).

From this study, the total of the achievement percentage categories for assessing hospital preparedness in facing COVID-19 in 15 Army Hospitals was obtained: fully functional categories with 100% achievement in hospitals in Sulawesi, Army Central Hospital, hospitals in Aceh, West Java and East Java, while fully functional categories with an achievement value of more than 79% but not reaching 100%: 8 hospitals in the regions of Sumatra, Bali, Sulawesi, Papua, Central Java and Kalimantan. Two hospitals in Kalimantan (78.1%) and Maluku (50.4%) are partially functional categories.

Achievement percentage categories were achieved through various efforts and collaboration with the supra system. The chief of army staff communicates every working day with all 68 army hospitals ranging from level 1 to level 4 and various first-level health service facilities through online meetings to determine how much is needed to overcome the COVID-19 pandemic.

Implementing the hospital preparation checklist from WHO to address the COVID-19 pandemic presents several challenges (WHO,2020); if it is fully implemented, it can help overcome the pandemic more quickly.

## 5. Conclusions

After implementing the 12 COVID-19 preparedness checklist from WHO, the recovery rate significantly increased while the death rate decreased. The WHO hospital preparedness checklist is beneficial in overcoming the COVID-19 pandemic quickly. However, in its implementation, many obstacles require attention and cooperation from various parties. Even though the hospital preparedness checklist is challenging to implement, the Gatot Soebroto Army Central Hospital and 14 Army hospitals in Indonesia received more attention from the Chief of army staff and the Army supra system by building a PCR laboratory and field hospital and directing personnel from members of the military command. Army headquarters pays excellent attention to Army Central Hospital and Level-2 Army Hospitals as referral centers in their respective regions. Attention from the supra system could support the implementation of the WHO checklist, which can be achieved at an adequate/high preparedness level in 13 hospitals and only two at a moderate/medium preparedness level. The intensive work among the Army Central Hospital Gatot Soebroto and all other Army Hospitals in Indonesia has resulted in new developments and several advantages that help with COVID-19 management.

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**Informed Consent Statement/Ethics approval:**
Human subjects: The absence of human subjects or tissue was confirmed by all authors in this study.
Animal subjects: The absence of animal subjects or tissue was confirmed by all authors in this study.

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# SARS-CoV-2 Vaccine Hesitancy and Acceptance Among Medical Students in Helmand, Afghanistan

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**Abstract**
Background/Objective: This study aimed to identify COVID-19 vaccine hesitancy among medical students in Helmand, Afghanistan, and its contributing factors. The findings will be presented to key healthcare organizations for peer review and used to develop a regional Risk Communication and Community Engagement (RCCE) strategy to increase national vaccine acceptance among medical students. Methods: This study employed a structured approach consisting of three steps. First, a paper-based Knowledge, Attitude, and Practice (KAP) questionnaire was developed and tested for efficacy and understanding. Second, using Yamane's formula to determine the appropriate sample size, a population-based stratified sampling method was employed to select 200 respondents from 937 medical students in 21 classes. Results: A survey conducted in February 2022 revealed a high percentage (38.6%, or 56 out of 145) of medical students hesitant to receive SARS-CoV-2 vaccination in Helmand, Afghanistan. Factors contributing to this hesitancy include a lack of information about COVID-19 vaccination, doubts about its adverse effects, and fear of long-term sequelae associated with immunization. Conclusion: The results of this study provide valuable insights for professors, policymakers, and health organizations to address factors contributing to COVID-19 vaccine hesitancy among medical students. Approaches such as RCCE campaigns, public awareness initiatives, and incorporating a dedicated vaccination chapter into the medical curriculum can minimize hesitancy and increase vaccine acceptance. Addressing vaccine hesitancy is crucial to prevent the spread of COVID-19 and protect the health of medical students at higher risk due to their proximity to infected populations.

**Keywords:** COVID-19, Vaccine Hesitancy, Medical Students, Vaccine Acceptance, COVID-19 Afghanistan

## 1. Introduction

In December 2019, a new virus, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), was discovered in Wuhan, China. This discovery was linked to a possible zoonosis-like event in a contaminated seafood market (Yang et al., 2020). The disease caused by SARS-CoV-2 was named "coronavirus disease 2019" (COVID-19) (Zahorec R, 2020). Despite control procedures such as restrictions, lockdowns, case tracking, and active

surveillance, the virus has rapidly spread worldwide (Yang et al., 2020). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic (Cucinotta & Vanelli, 2020). Unfortunately, as of October 3, 2023, SARS-CoV-2 still infects humans with severe or less severe variants. According to a report based on data from the Johns Hopkins University Coronavirus Resource Center, there have been a total of 676,609,955 confirmed cases of COVID-19 and 6,881,955 deaths worldwide (*COVID-19 Map - Johns Hopkins Coronavirus Resource Center*, n.d.)

The first case of COVID-19 in Afghanistan was reported on February 24, 2020, in Herat, a western province bordering Iran. The patient was a 35-year-old man who returned from Qom City in Iran (Nemat, Asady, et al., 2021). Notably, SARS-CoV-2 entered Qom City in the third week of February 2020 (Delirrad & Mohammadi, 2020). According to the WHO COVID-19 dashboard, from January 3, 2020, to October 12, 2023, there have been 226,220 confirmed cases of COVID-19 in Afghanistan, with 7,950 deaths (Afghanistan: WHO Coronavirus Disease (COVID-19) Dashboard with Vaccination Data | WHO Coronavirus (COVID-19) Dashboard with Vaccination Data, n.d.-a).

However, no comprehensive management is currently available for COVID-19. Scientists have developed and tested several vaccines to activate the immune system against SARS-CoV-2 (Bian et al., 2021). The aim of these vaccines is twofold: first, to protect individuals from severe COVID-19 infections, hospitalization, and death; and second, to prevent and control the spread of the virus. Vaccine discovery has historically played a crucial role in public health by significantly reducing disease morbidity, mortality, and transmission (Bian et al., 2021; Plotkin & Plotkin, 2011). However, despite the importance and effectiveness of vaccines, there are barriers to achieving this purpose, such as vaccine hesitancy, which remains a significant challenge (MacDonald et al., 2015). Vaccine hesitancy refers to a delay in accepting or refusing vaccines despite their availability(MacDonald et al., 2015). It is considered a significant barrier to eradicating vaccine-preventable diseases and was declared as one of the ten significant threats to global health by the WHO in late 2019; addressing vaccine hesitancy is crucial for global public health, individual well-being, and overall social and economic prosperity (*Ten Threats to Global Health in 2019*, n.d.).

To fight hesitancy, targeting medical students is essential for several reasons. They are the future of the medical field, frequently interact with patients and their families, play a vital role in addressing vaccine hesitancy, and are uniquely positioned to bridge the gap between the medical community and the public (Lucia et al., 2021). Therefore, understanding vaccine hesitancy levels and factors among medical students can improve vaccination acceptance and campaign success (Machingaidze & Wiysonge, 2021; Venkatesan et al., 2022).

### *1.1 COVID-19 Vaccine Acceptance in Afghanistan and Other Countries*

The acceptance rate of COVID-19 vaccines varies significantly across countries, with China reporting a high % acceptance rate of 90% compared with Russia's 55% (Lazarus et al., 2020). Moreover, studies in low-income countries have reported an average vaccine acceptance rate of 80.3% among the general population (Machingaidze & Wiysonge, 2021).

Medical students also exhibit varying degrees of vaccine hesitancy in different regions, including 10.6% in India, 13.9% in Italy, 23% in the USA, 41.2% in Ethiopia, 46% in Egypt, and 58.2% in Wuhan, China (Barello et al., 2020; Gao et al., 2023; Jain et al., n.d.; Lucia et al., 2021; Mose et al., 2022; Saied et al., 2021).

Afghanistan, one of the world's poorest countries, faces a high incidence of vaccine hesitancy for complex reasons (Harapan et al., 2022; SAMADİ et al., 2023). It is worth mentioning that Afghanistan is one of the two countries that are still endemic to polio, with cases primarily concentrated in rural areas bordering Pakistan (Ahmadi et al., 2020; Bjork et al., 2023; O'Reilly et al., 2012). Immunization coverage of polio and other vaccines is challenging in these regions, contributing to high vaccine hesitancy (Ahmadi et al., 2020). A recent population-based study in Afghanistan revealed that 63% of the general population was willing to receive the COVID-19 vaccine, whereas 37% expressed hesitancy (Nemat, Bahez, et al., 2021). Factors contributing to vaccine refusal or delay in

Afghanistan include illiteracy, lack of awareness, security concerns, mistrust in efficacy, misinformation, safety concerns, and fear of adverse effects (Ahmadi et al., 2020; Nemat, Bahez, et al., 2021; Wardak et al., 2021).

According to the World Health Organization (WHO), as of October 25, 2023, the following COVID-19 vaccination data have been reported for Afghanistan (*Afghanistan: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data*, n.d.-b):

- In total, 21,893,320 vaccine doses were administered.
- 18,3385,310 people were vaccinated at least once.
- A total of 17, 607, 688 individuals were fully immunized.

In this study, we aimed to identify vaccine hesitancy levels and factors among medical students in Helmand, Afghanistan. We aimed to support vaccination acceptance and campaign success by focusing on this group. Health organizations can develop strategies to improve vaccine acceptance and public health outcomes in Afghanistan by identifying factors contributing to vaccine hesitancy.

## 2. Materials and Methods

A cross-sectional study was conducted using stratified sampling to collect data. This method was chosen because of the heterogeneous nature of the population and the need to estimate parameters within different subgroups, compare them, and reduce the sampling errors. The study participants were from 21 other classes or subgroups of medical students at Bost University in Helmand, Afghanistan, the largest university in the country's southern region. This provided a convenient setting for our research.

The sample size for this study was calculated using Yamane's formula (Adam, 2020). With a confidence level of 95%, margin of error of 6.3% (Suresh & Chandrashekara, 2012), and population proportions of 50%, a sample size of 200 was determined from 937 students. Among the 200 participants, 45 (22.5%) were female and 155 (77.5%) were male.
Yamane's Formula 1967: n = N/{1+N(e)(2)}
Where:

- n is the sample size
- N is the population size, which is 937
- e is the margin acceptable error, 6.3% (Suresh & Chandrashekara, 2012)

$$n = \frac{937}{1 + 937(6.3)^2} = 198.6 \approx 199$$

After calculating the sample size, a Knowledge, Attitude, Practice (KAP) questionnaire assessed the medical students' knowledge, attitude, and practice regarding vaccination. The questionnaire was initially created in English with the Medical Student Council. It was then translated into the local language (Pashto) and presented to and approved by the University of Bost Ethical and Research Committee on Meeting Number 7, dated January 31, 2022; Registered #: BostEthic-0744.

Before the data collection, a pilot study was conducted to test the questionnaire. The data collection process involved paper-based questionnaires distributed to the respondents for self-reporting. The survey lasted three weeks, every Saturday, from February 05, 2022, to February 26, 2022. Of the 200 self-reported questionnaires distributed, 55 were flagged and excluded from the analysis. The overall survey universe consisted of 145 correctly answered questionnaires. For analysis, an Excel database was created by an IT consultant. The database was crucial for analyzing the 16 knowledge, attitude, and practice questions. Before analyzing the complete dataset, a pilot test was conducted to ensure accuracy and identify potential issues.

In addition to the Excel database, a Google Form survey was used to analyze the collected data further. This versatile survey form facilitated the organization and interpretation of the dataset, allowing for a comprehensive

evaluation of the responses. By employing a multidimensional approach that incorporated the Excel database and Google Forms survey, the IT consultant ensured efficient analysis and enhanced the overall effectiveness and reliability of the research findings.

*2.1 Ethical consideration*

Before the data collection, the participants were given a brief orientation, and the study's objectives were explained. Additionally, the participants were assured that their confidentiality would be protected. Written consent was obtained from all participants, and those unwilling to participate had the right to refuse and were not obligated to participate in the study. No financial or other incentives were provided to students to complete the survey.

**3. Results and Discussion**

The overall goal of the survey was to identify hesitancy and the factors and circumstances that caused hesitancy among medical students. A total of 200 participants were targeted, but unfortunately, there were 55 flagged records among the sample results, resulting in only 145 records being considered for the analysis; the survey response rate was 72.5%.

*3.1 Demography of the students in the sample*

Of the 145 respondents, 117 were male, and 28 were female (80.7% male and 19.3% female). In terms of age, 84.13% (122 out of 145) (were aged between 19 and 26 years, while the remaining 15.8% (23 out of 145) were below 19 or above 26 years.

The study revealed that 55.2% (80 participants) of the medical students were not vaccinated (Table 1), and 44.8% (65) of the students responded that they had been vaccinated with the SARS-CoV-2 vaccine.

Table 1: Percentage of vaccinated students by sex.

| Total Participants (145 students) | Male | Female | Total |
|---|---|---|---|
| | 117 (80.7%) | 28 (19.3%) | 145 (100%) |
| Non-Vaccinated | 68 out of 117 | 12 out of 28 | 80 (55.2%) |
| Vaccinated | 49 out of 117 | 16 out of 28 | 65 (44.8%) |

*3.2 Hesitancy of students under the sample*

The study also showed that for multiple reasons, 56 of 145 surveyed (38.6% of the total surveyed) medical students hesitated with the SARS-CoV-2 vaccine. The hesitant students were from pre-clinical (1-3 years of medical faculty) and clinical (4–7 years of medical faculty) backgrounds.

- Pre-clinical studies students: 44
- Clinical studies students: 12

The study showed that 44 out of 56 hesitant students in their pre-clinical studies were more willing to be vaccinated, and 12 out of 56 hesitant students were in their clinical studies. Hence, we can infer that the clinical studies students (with more years of study) were more eager to receive the vaccine than the pre-clinical students. This may be because the latter group had less medical knowledge.

*3.3 Information regarding COVID-19 attitudes of students in the sample.*

Of the 145 respondents, 88 (60.7 %) received information regarding the SARS-CoV-2 vaccine at non-biased, non-anti-vax sites. Hence, they had positive attitudes toward vaccination, while 39.3% (57 out of 145) responded that they did not have sufficient overall information about SARS-CoV-2. Hence, they were hesitant about vaccination

(Fig. 1). According to their attitudes and practices, they may receive the SARS-CoV-2 vaccine if they obtain complete and comprehensive information regarding the SARS-CoV-2 vaccine.

Most of the respondents got their information and understanding regarding the COVID-19 vaccine as well as anti-Vax propaganda against the vaccine from 1) social media such as Facebook, Twitter, and radio, 2) information through healthcare workers, and 3) information through community people.

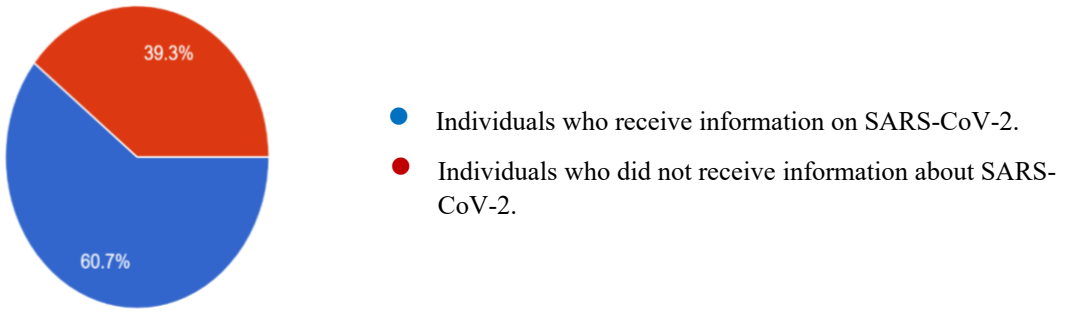


Figure 1: Information about SARS-CoV-2 vaccination

Half of the sample students (73 out of 145) were trying to decide whether to reject or accept the vaccination; they responded that it may be vital for them to be health workers. Still, they were not confident enough, and the study showed that i) 37.2% of students agreed that vaccination is vital for them, and ii) 12.4% were against the vaccination and selected the "No, it's not important for me as a health care worker" option. (Fig. 2)

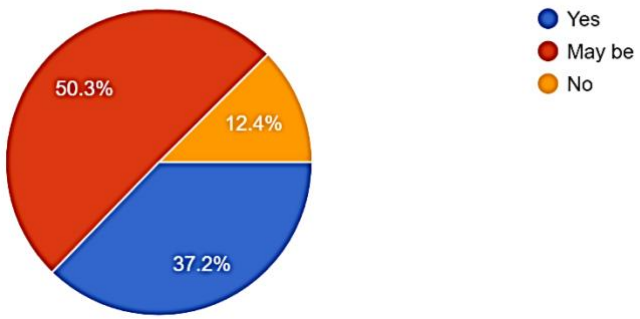


Figure 2: Importance of SARS-CoV-2 Vaccination in Participants.

Comparing the study findings with similar studies conducted globally, medical students in southeast Michigan, USA exhibited a 23% unwillingness to receive the COVID-19 vaccine (Lucia et al., 2021). Comparable hesitancy rates have been observed among medical students in Italy (13.9%), Egypt (46%), and India (10.6%) (Barello et al., 2020; Jain et al., n.d.; Saied et al., 2021). Likewise, research conducted in Wuhan, China, and Ethiopia revealed vaccine hesitancy rates of 58.2% and 41.2 %, respectively (Gao et al., 2023; Mose et al., 2022). Surprisingly, our study's data revealed a concerning rate of vaccine hesitancy of 38.6%, highlighting the difficulties in achieving adequate vaccination coverage and controlling the spread of COVID-19.

Of the 56 hesitant students surveyed, 18 students rejected the SARS-CoV-2 vaccine. This accounted for 12.2% of the 145 surveyed students, while the rejection rate among Egyptian students was 6% (Saied et al., 2021). The remaining 38 out of 56 hesitant students (26.2%) did not respond clearly, stating that they may have considered getting the vaccine after obtaining unbiased information (Table 2).

Table 2: Vaccine acceptance and rejection among students

| Total survived students | Hesitant students | | Non-hesitant students |
|---|---|---|---|
| 145 (100%) | 56 (38.6%) | | 89 (61.4%) |
| | 18 (12.4%) | 38 (26.2%) | |
| | Will not get vaccine after information, complete rejection | Maybe get a vaccine after getting the information | |

### *3.4 Reasons behind Hesitancy and Rejection of the COVID-19 Vaccination*

The reasons for hesitancy and rejection of the COVID-19 vaccination varied (Fig. 3). Still, the most prevalent were i) a lack of public awareness and information about SARS-CoV-2, ii) adverse and side effects after vaccination (particularly the severe fever that is equivalent to COVID-19's fever), and iii) propaganda about unhealthy sequelae that SARS-CoV-2 may cause after vaccination. Other less common reasons made the students hesitant.

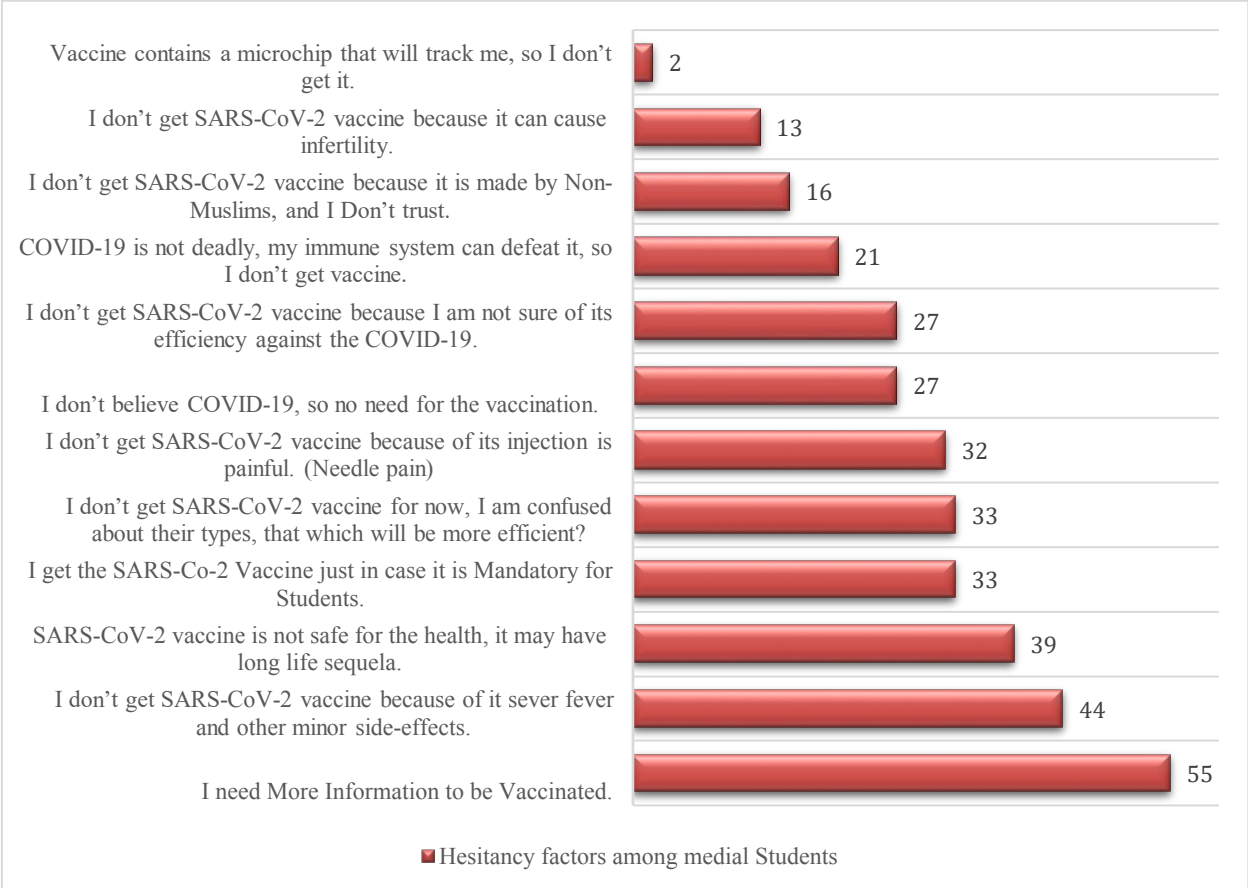


Figure 3: Reasons behind vaccine hesitancy

The reasons for vaccine hesitancy were similar to those in studies conducted in India and Egypt. In India, factors include a lack of awareness, vaccine safety and efficacy concerns, and distrust in government agencies (Jain et al., n.d.). In Egypt, hesitancy is due to doubts about vaccine safety, fear of adverse effects, effectiveness, long-term genetic effects, insufficient trust in vaccination sources, and fear of COVID-19 infection (Saied et al., 2021). Our study found that media campaigns on SARS-CoV-2 greatly influenced vaccine hesitancy and acceptance. Students who were educated about the virus and relied on trusted social media were more willing to receive vaccination

than those exposed to anti-vax propaganda. Social media was the primary source of anti-vaccine information for hesitant students, followed by negative rumors regarding side effects and effectiveness.

Several limitations may have affected the results of the study. First, the findings apply only to medical students and may not be generalizable to other populations. Additionally, the sample size could have been larger because of the lack of participation from some students. Moreover, 55 questionnaires were flagged and excluded from the analysis because of incomplete or improper answers, reducing the overall sample size. Finally, the study was conducted when COVID-19 vaccines were not widely accessible in all healthcare facilities.

## 4. Conclusion

In conclusion, this research highlights a concern (38.6%) of hesitant students towards SARS-CoV-2 vaccination, attributed to factors such as lack of information, concerns about adverse effects, and fear of long-term sequelae. It is crucial to address this hesitancy by incorporating a dedicated chapter on vaccine hesitancy in the educational public health curriculum, specifically targeted toward students, to promote informed decision-making and prevent unintentional participation in anti-vax groups. Achieving a high coverage of the SARS-CoV-2 vaccine is essential for combating the pandemic and managing it as an endemic event. Medical students play a significant role in convincing individuals to be vaccinated, necessitating the study of hesitancy factors and implementing a strong risk communication and community engagement (RCCE) strategy to increase vaccination coverage. Failure to address this issue may jeopardize the effective implementation and monitoring of COVID-19 vaccination programs. We urge professors, health policymakers, the Afghanistan Ministry of Public Health, the health cluster, and other relevant health organizations to proactively address hesitancy towards the SARS-CoV-2 vaccine, aiming for a healthy Afghanistan population by reducing COVID-19 incidence, disease severity, and related deaths.

**List of Abbreviations:**
COVID-19: Coronavirus disease 2019
SARS: Severe acute respiratory syndrome.
RCCE: Risk communication and community engagement
MD: Doctor of Medicine
WHO: World Health Organization
KAP: Knowledge, Attitude, and Practice

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**Data Availability:** The dataset is available and is presented upon request.

**Conflict of interest:** The authors declare no conflict of interest.

**Ethical consideration:** Before the data collection, the participants were given a brief orientation, and the study's objectives were explained. Additionally, the participants were assured that their confidentiality would be protected. Written consent was obtained from all participants, and those unwilling to participate had the right to refuse and were not obligated to participate in the study. No financial or other incentives were provided to students to complete the survey.

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# Integrated, Decentralized Wastewater Management Use to Improve the Environmental Health of Khartoum Locality Sudan

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**Abstract**
The management of water resources and the related disposal of wastewater are essential for human existence and the advancement of contemporary society. Collecting and managing wastewater has a significant effect on local and global economies as well as the environment. Innovation in the field of the environment is of utmost importance in reducing the environmental impacts on systems and in making them more sustainable economically, environmentally and socially. Decentralization is considered an appropriate solution to sustainability problems in liquid waste management programs because it focuses on treating liquid waste on-site, recycling it locally, and taking advantage of the local resources available in domestic wastewater. This research analyzes the needs, appropriate technical methods, and support for water management through decentralized systems. Three considerations will be used to support the choice of a decentralized wastewater treatment system in the Khartoum Locality: $106,000,000. According to the BioWin results, the effectiveness of each alternative household wastewater treatment was comparable. Software such as MapInfo, GPS Area Calculator, BioWin, and GIS was used to reach the targets. Additionally, the results revealed that the decentralized wastewater treatment method, considering its costs, land requirements, and slope effects on the environment, is preferable to centralized wastewater treatment systems. These results serve as a guide for choosing the best wastewater treatment option to increase access to safe sanitation and to integrate decentralized wastewater management to upgrade and improve the environment in the Khartoum Locality.

**Keywords:** Wastewater Management, BioWin, MapInfo, Recycling, Environmental Impacts, Environmental Consequences, Decentralized

## 1. Introduction

Sustainability is challenged by urban deterioration, especially in fast-expanding places, such as Khartoum, where population density limits access to sanitary facilities (Capodaglio, et al., 2017). To guarantee appropriate management and accessibility, Article 6 of the Sustainable Development Goals mandates the support and modernization of wastewater treatment systems and sanitation services (UNDP, 2017). Urban decay presents sustainability issues, particularly in fast-growing places, such as Khartoum, where access to adequate sanitation is constrained due to a smaller population (UNDP, 2017). Goal 6 of the United Nations Sustainable Development Goals ("Clean Water and Sanitation") It is expected to achieve passable and justifiable access to hygiene and environmental health services in the year 2030, and at the same time reduce the rate of production of untreated liquid waste by half with the increase in recycling services and safe use at a high level globally, as at the present time there are no less than 1.8 billion The world deals with drinking water sources that are contaminated with human waste, while more than 1.7 billion people live in river basins, and more than 80% of the liquid waste resulting from human activity is disposed of without any treatment (WHO, 2019). According to the WHO 2019, 3800 children under the age of five die every day from unhygienic circumstances, inadequate hygiene, and tainted water, with the cost to nations reaching 5% of their GDP, whereas simple sanitation initiatives pay for themselves five times over (Risch, et al., 2015). The gathering and management of liquid waste have a substantial effect on local and global environmental and economic levels (UN, 2022) Owing to limited sanitation and wastewater treatment facilities, Khartoum State faces considerable hurdles in wastewater treatment and environmentally friendly growth (UNEP, 2002). Despite the inhabitants' tolerance for septic tanks, World Bank research demonstrates that septic tank discharge in the Khartoum Locality causes water diseases, flies, mosquitoes, and pollutes shallow aquifers. According to Khartoum Locality's 2018 National Environmental Standard, residential BOD emissions were higher than the national average. Given that 26% and 46% of the world's population lack access to clean water and sanitary facilities, respectively, these necessities are essential for promoting public health (CBS, 2018). Decentralization is becoming more popular in outlying areas as cities relocate to the countryside, feeding 25% of the US population more than ten years ago, while also facilitating future growth (Ministry of Irrigation, 2013) Sudanese officials are hesitant to discharge treated wastewater into the Nile River (Jones, et al, 2012). despite their technical feasibility. There is a scarcity of water resources in North Africa and the Middle Eastern countries. There is an immense need to reuse wastewater after adequate treatment (El Moll, 2023). The collection of wastewater significantly influences the environment both globally and locally. One solution to achieve sustainability is the decentralization of wastewater management (Capdaglio, 2017). Scarce empirical evidence is available on the decentralization of wastewater management in Khartoum, Sudan. Originality and novelty lie in improving the environment and attaining sustainability in terms of economic, environmental, and social terms, as well as environmental health. This is one of the pioneer studies which has contributed towards water management of decentralized system in Sudan. This study aimed to enhance water and human health protection in Khartoum.

## 2. Method

### *2.1 Study area*

Khartoum locality is located geographically at the confluence of the Blue Nile and the White Nile. It is bordered by the Jebel Aulia locality to the west, Al-Jazeera State to the south, and Blue Nile to the east (Fig.1). Khartoum is relatively flat at an elevation of 385 m. The total area of the locality is 135.33 km2. The population is 834,573 people.

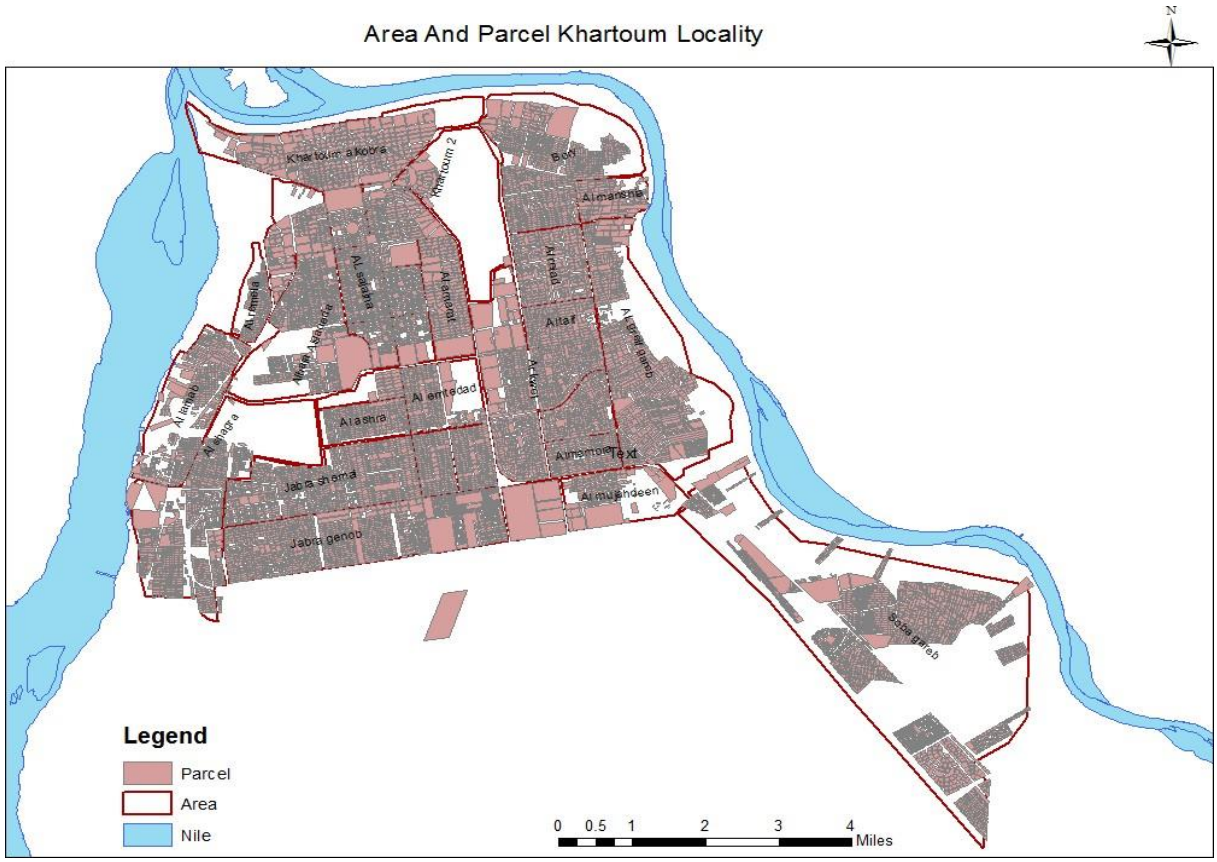


Figure 1: Khartoum Locality Area

*2.2 Data collection*

This study developed and modeled a wastewater treatment system, highlighting social and environmental challenges, using data from the study area, raw sewage characteristics, and daily wastewater.

*2.3 Treatment plants*

Several factors, such as environmental, economic, and social criteria, should be considered when evaluating the efficacy of wastewater treatment systems to choose the best system. Using tools such as MapInfo, GPS Area Calculator, BioWin, and GIS, this study analyzed the land requirements, expenses, and wastewater treatment systems of the Hospital Soba University Plant and Arkwet Hospital Al-Galeb Plant.

*2.4 Data analysis*

The study utilized various tools to evaluate the survey data, focusing on the predicted population, plant types, and wastewater treatment plant design capacity. An analysis flowchart for this investigation is shown in Fig (2)

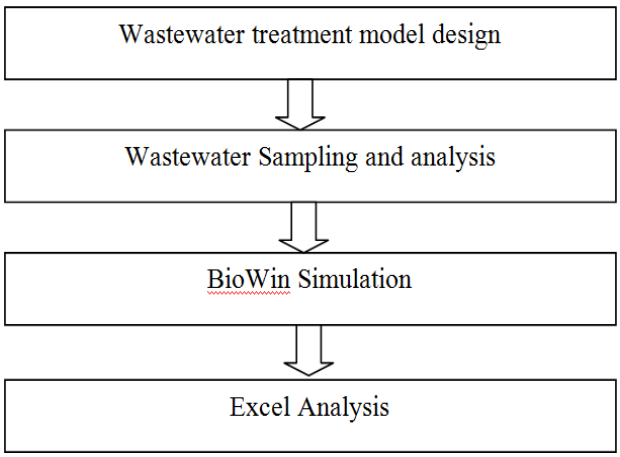


Figure 2: An analytical diagram for the best design of waste water system in Khartoum locality

*2.5 Decentralized system*

Using the decentralized system for each area independently, the treated water inside each region was drained to irrigate the grass and trees, and the remaining water was drained to the Nile in accordance with the necessary Sudanese requirements. The amount of wastewater that needs to be treated in Table 1in the area of Khartoum. Khartoum Locality Master Plan for Sewage Treatment Facilities and Sewerage Networks Disposal and reuse

*2.6 Scenarios*

Specific guidelines are adhered to for pipeline routes and WWTP locations, such as avoiding new lifting stations, removing pumping stations, and avoiding opposing slopes. Each area has its own supply owing to a decentralized system that drains treated water for grass and trees and dumps the leftover water into the Nile. To irrigate agricultural areas around Khartoum, 25% cubic meters of water are needed each day or roughly 24666.82 m3/day. Geographical Information System (GIS): The locations of the treatment facilities, pumping stations, and sewer network were chosen using GIS. The positions suggested in Figure 3 depict the locality around Khartoum's proposed initial location for wastewater treatment plants. The well-known computer program.

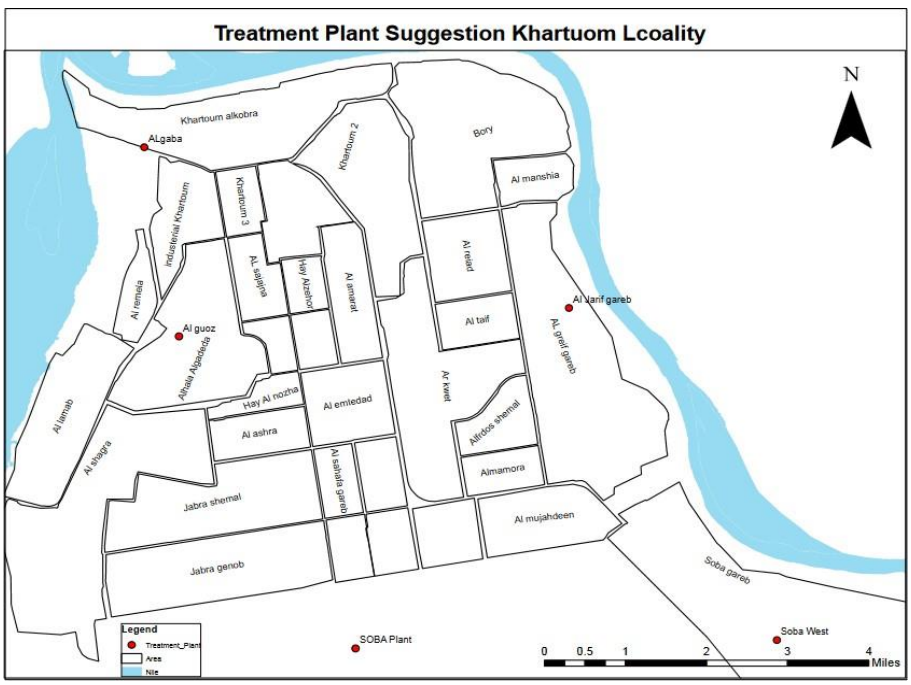


Figure 3: Suggested preliminary location for treatment wastewater plants in the Khartoum locality

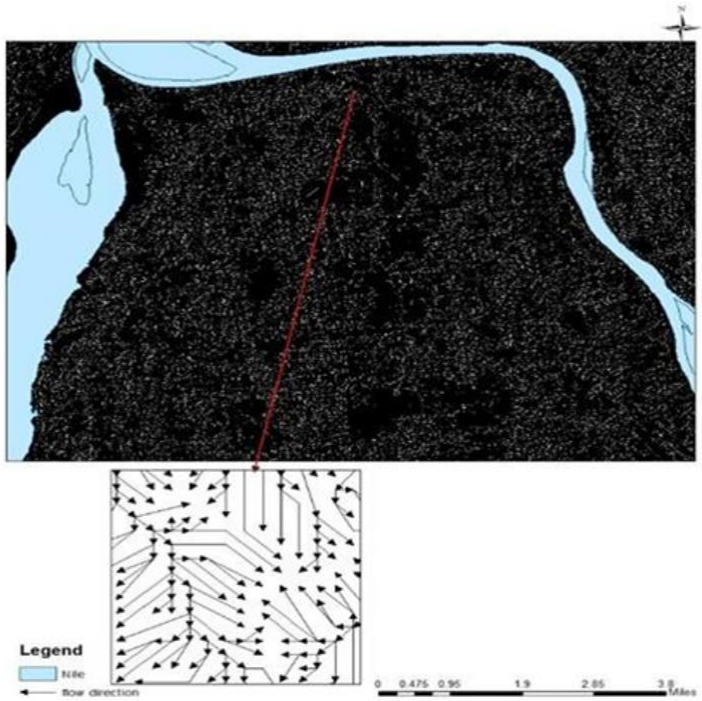


Figure 4: The natural slopes are towards the Nile River

*2.7 Bio Win Simulation*

Bio Win (version 6.0), created by EnviroSim Associates, is used to simulate the wastewater treatment process. Using physical, biological, and chemical process models, BioWin is used to build, improve, and optimize all types of wastewater treatment plants (Balkema, 2002). This study employed BioWin to generate two liquid waste treatment methods, with every method running independently in the BioWin model. Outcomes were examined to determine if they were effective and if the effluent parameters fulfilled Khartoum's water pollution guidelines. If the effluent concentrations did not reach the limits after five days, the parameters were changed, and the imitation was frequented until the sewage met the criteria.

*2.8 Wastewater Estimation*

Generally, it is assumed that 80% is ordinary water of the total water contained in the use of ordinary water is discharged as treated water according to ordinary water engineering. (Fane, 2005), and the introductory possibility of explosion of wastewater management in the Khartoum Locality. Consequently, the internal liquid waste movement was considered, as shown in Table (1) as follows: On behalf of defining the size of wastewater treatment plants, approximately five stations were designed in the study. The number of upcoming people in 2048 is estimated to be 1,855,998 people; consequently, in this study, a family size of seven persons was adapted for computing the liquid waste run for all stations. The required number of liquid waste treatment plants and their design capacities depend on population expectations and the types of plants that are designed (Capodaglio, 2016).

Table 1: The quantity of wastewater to be treated and the available empty agricultural lands in Khartoum locality

| No | Name of plants | Open irrigated space (acre) | Waste water $m^3$/day | Design $m^3$/day | Unit price ($) | Station cost ($) |
|---|---|---|---|---|---|---|
| 1 | Soba west | 682.65 | 5483.5 | 10000 | 1000 | 10000000 |
| 2 | AL-Jerif gareb | 1033.3 | 19685.23 | 20000 | 800 | 16000000 |
| 3 | Soba Plant | - | 19685.23 | 20000 | 800 | 16000000 |
| 4 | Al ghaba (forest) | 286.35 | 35318.304 | 40000 | 800 | 32000000 |
| 5 | Al Guoz | 412.28 | 38076.88 | 40000 | 800 | 32000000 |
| 6 | Total | 1897.9 | 118249 | 130000 | - | 106000000 |

*2.9 Sustainable Design of New Decentralized Wastewater Treatment systems*

The technology that can be implemented in distributed systems includes a wide range of operations that vary in complexity and sophistication. In terms of cost, advanced technologies are quickly becoming comparable to centralized applications (Istenic, et al, 2015). Decentralized facilities are currently easy to control remotely, which helps in the process of operation and maintenance. The deficiency of consistent technologies for inaccessible observation constitutes a thoughtful problem for decentralization, which leads to unsustainable requirements for workers and unreliable treatment (Chong, et al, 2013).

Processes performed in effluent treatment tanks lead to a decrease in the conversion of organic components. Estimates show that approximately half of the organic matter may be transformed into effluent treatment tanks, contingent on the temperature of operation and preservation. Applications of liquid waste treatment systems allow the partial reuse of water, which has some important limitations (WHO, 1992. Ormiston, et al, 2004).

Two types of decentralized systems that are available in developed and developing nations make up wastewater treatment systems under consideration for decentralized systems. Because they are simple to use and maintain, very effective, and the right technology, two in particular, stabilization ponds and MBBR, were chosen and used for the analysis of the system shown in Figures 3, 4, and 5 (among many others). The three wastewater treatment models considered in the Bio Win simulations took into account.

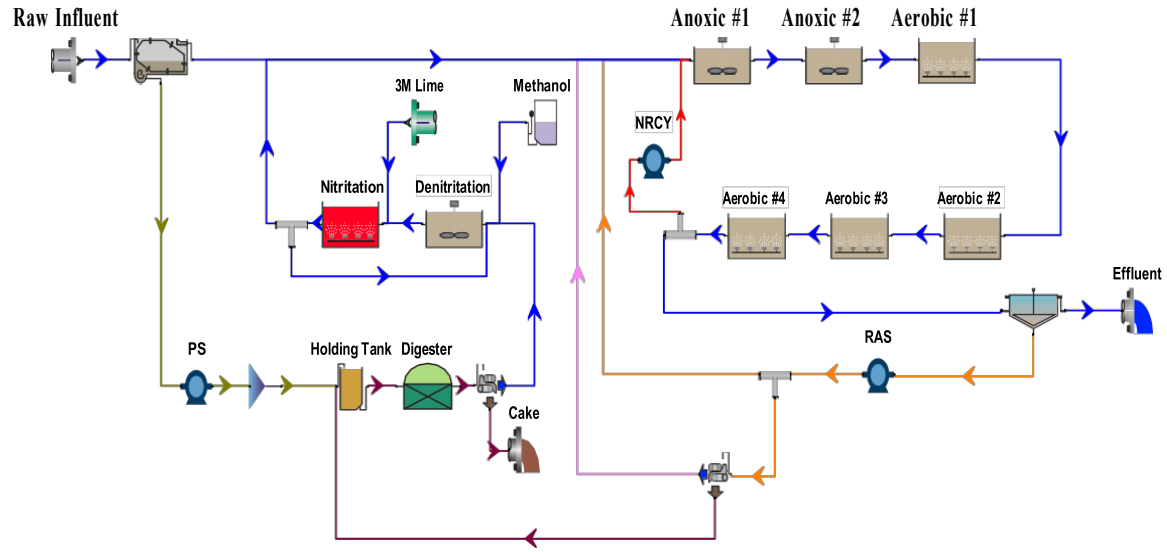


Figure 5: Al-Jarif ghareb treatment plant with design capacity 20.000 m3/day

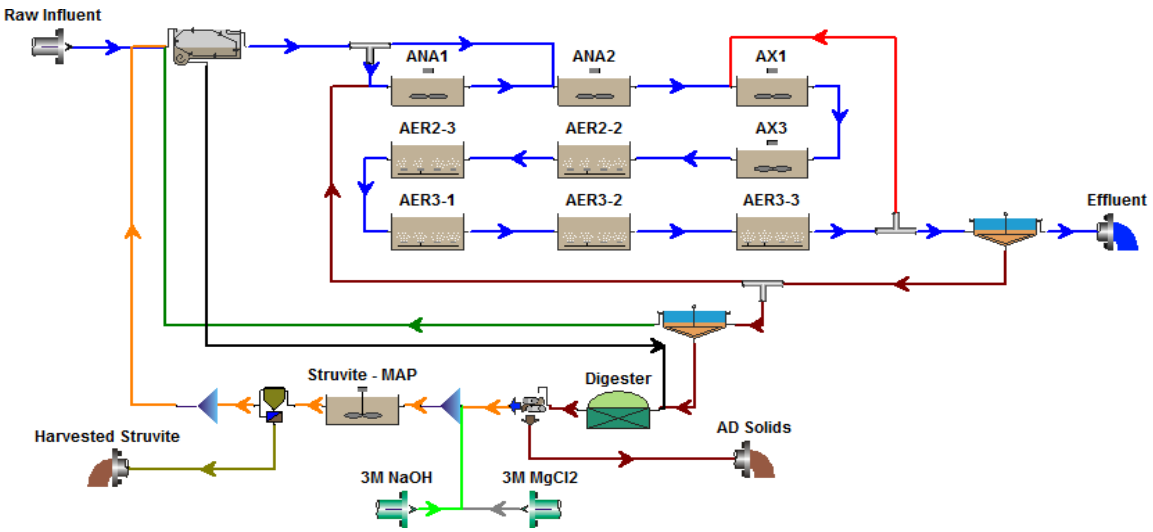


Figure 6: West Soba treatment plant with design capacity 10,000 m3/day

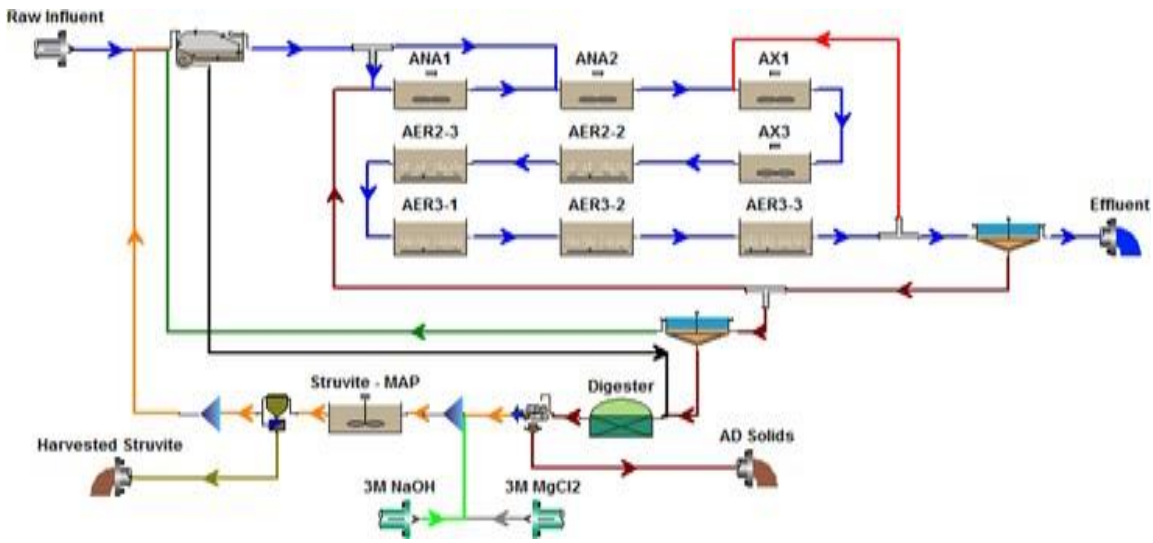


Figure 7: Al-Guoz treatment Plant with design capacity 40000 m3/day

We carefully examined and used the following recommendations when creating the three models: Improvement of On-Site Health Strategies (USEPA, 1980). On-site liquid waste Structures: Project and Administration Guide, on-site liquid waste Management System Manual, Water and Wastewater Calculations Manual are some of the manuals that are available. Engineering wastewater treatment (USEPA, 2014, Andrea, 2017). Engineers working in this field of research are key guides for designing sanitation and wastewater treatment systems.

## 3. Results

Table 2: Representing the quantity of wastewater to be treated and available for agricultural land and design plant of decentralized treatment plant in Khartoum Locality

| S# | Plant | Design Plants $M^3/d$ | Area Acre | Water needs for each area $M^3/d$ | Wastewater $M^3/d$ |
|---|---|---|---|---|---|
| 1 | Al-Jarif West | 20000 | 1033.3 | 9033.7 | 19685.23 |
| 2 | Soba West | 10000 | 1365.3 | 11796.13 | 5483.5 |
| 3 | Al-Qaba | 40000 | 572.6 | 4910.1 | 35318.3 |
| 4 | AlGuze | 40000 | 824.6 | 7277.8 | 38076.9 |
| 5 | Soba pLant | 20000 | - | - | 19685.23 |
| 6 | Total | 130000 | 3795.7 | 32958 | 118249 |

From Table 2, it can be seen that the al-Jarif West and Soba plants have more wastewater m3/d (19685.23), followed by AlGuze which is 38076.9 m3/d and Soba West (5483.5 m3/d respectively.

### *3.1 Requirements for the Discharge of effluents into Surface Waters*

The Sudanese Standards Organization created a specification for wastewater reuse that is distinct from the international standards. While the laws are the same in Europe and the US, they differ in other countries, such as India. While the European and American regulations are 15 mg/L, Western countries recommend a BOD5 value of 25 mg/L for water before it is dumped into rivers. The Nile River's capacity and flow rates are incomparable to those of the Rhine or Thames.

Table 3: Daily Discharges of the Nile Rivers and River Thames

| River Gauging Location | Daily Minimum Flow on Record in million $m^3$ | Daily Average Flow in million $m^3$ | Daily Maximum Flowin million $m^3$ |
|---|---|---|---|
| River Nile<br>(Gauge located Further downstream of Khartoum) | 40 M $m^3$ or 463 $m^3$/sec | 185 M $m^3$or 2141 $m^3$/sec | 910$Mm^3$or10532$m^3$/sec |
| Blue Nile<br>(Gauge located at Khartoum) | 0.25$Mm^3$ or2.89$m^3$/sec | 119$Mm^3$or1377$m^3$/sec | 955$Mm^3$or11053$m^3$/sec |
| White Nile<br>(Gauge located at Khartoum) | 55 $Mm^3$ or 637 $m^3$/sec | 75 $Mm^3$ or 868 $m^3$/sec | 175$Mm^3$or 2025 $m^3$/sec |
| River Thames<br>(Gauge located at Teddington) | 0.846$Mm^3$ or 10 $m^3$/sec | 6.74$Mm^3$ or 78 $m^3$/sec (London:65.8 m3/s) | 91.50$Mm^3$or1059$m^3$/sec |

*3.2 Bio Win Simulation*

The concentrations of BOD, COD, and TSS in the two wastewaters after the BioWin simulations are shown in Table (3). Simulations were run for five days to determine whether the wastewater treatment models matched the water pollution control guidelines set by the Khartoum Locality. The adjustable parameters were changed, and the process was repeated until the standards were met.

Table 4: Results of studies conducted at two plants for wastewater treatment

| Test | Unite | Soba Hospital University Plant | | BioWin | Arkwet Hospital Al-galeb Plan | | BioWin |
|---|---|---|---|---|---|---|---|
| | | In let | Out let | Out let | in let | Out let | Out let |
| **BOD** | Mg/L | 566.6 | 360 | 6.64 | 250 | 90 | 6.64 |
| **COD** | Mg/L | 600 | 440 | 53.39 | 560 | 256 | 53.39 |
| **TSS** | Mg/L | 4550 | 700 | 19.51 | 220 | 20 | 19.51 |

Laboratory evaluation confirmed that stations operate beyond the environmental restrictions of Khartoum Governorate's water resource protection system, and wastewater quality exceeds permissible limits. De Graaff et al. reported that decreases in total Chemical Oxygen Demand (COD) up to 80–90% were described, and straight at lower temperatures (above 20 _C), average exclusions of approximately 70% could be expected.

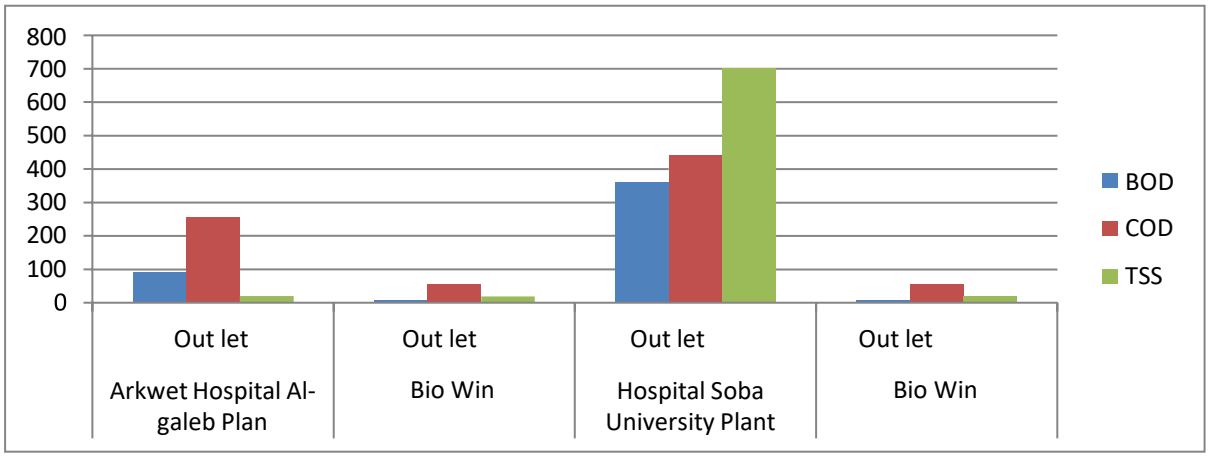


Figure 8: Comparison of plant efficiencies before and after designing BioWin

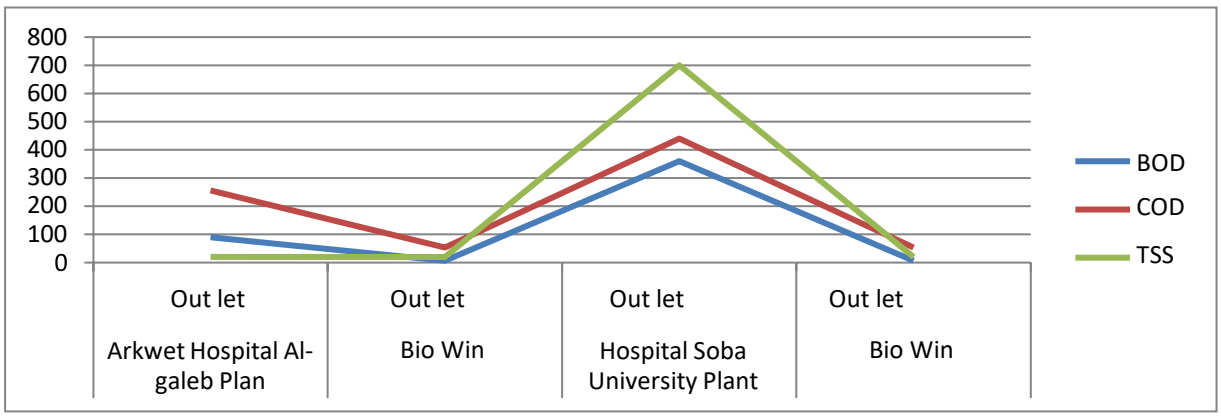


Figure 9: The results of the laboratory examination, which revealed that all stations operate beyond the environmental limitations of the system permitted to protect the water resources of the Khartoum Locality and that the quality of wastewater exceeds the authorized environmental limits.

## 4. Discussion

Our study shows replicated sewage BOD, COD, and TSS concentrations in the two wastewater treatment models. The three wastewater flow parameter limitations for controlling domestic wastewater release were BOD: 15 mg/L, COD: 75 mg/L, and TSS: 30 mg/L. Therefore, none of the focuses met the Khartoum local water pollution standards for domestic wastewater and Khartoum local control standards for domestic wastewater. In terms of the flatness of the land, it tends to the north, that is, at the level of the Nile, and this reduces the cost of construction at the level of the sewage network, land requirements, there are open spaces and public areas within the Khartoum locality, which must be irrigated with treated wastewater. Although the methods now adapted for individual services have contributed to significant development in public health, sustainable solutions remain a requirement in light of the increasing need for resources due to the increase in population (Ma, et al,2017. US EPA 1997).

Liquid waste is classified into four types of services according to the primitive classification of water management, each of which is managed according to specific rules and depends on the others. By assessing complex water issues in an integrated manner, any comprehensive water system can be sustainable and balanced with local economic and environmental services (Massoud, et at. 2009). The importance of central water systems lies in unification, which allows them to meet the needs of water and quality standards on a large scale. They are also subject to a certain degree of financial, organizational, and technical stagnation. Studies on acute water shortages and related factors have focused on water reuse.

It is difficult to benefit from treated water in the case of a central sewage treatment system due to the increased operational cost, because the central treatment plants are outside the region, while it is possible to benefit from it in the case of a decentralized system. Discharging treated water in excess of the region's needs into the Nile River and its tributaries. But in terms of cost, the decentralized system appears less expensive, so it is easier to implement, while the centralized system shows high cost. There are great benefits the decentralized infrastructure can provide by spreading the risks of drought and miasma between deferent locations.

The US Environmental Protection Agency (EPA) has recognized that "decentralized wastewater systems may provide a cost-effective and long-term option for meeting public health and water quality goals, particularly in less densely populated areas" (Tchobanoglous, et al, 2003). According to the questionnaire (trying to find solutions to the sewage problem in Khartoum State), 79.4 % of the population rejects the establishment of a sewage station in the neighborhoods, while 20.6 % agree. To establish a sewage plant in the neighborhood. Therefore, the government must intervene and solve the problem in accordance with the higher interests of the region. The sultan in Khartoum wants open spaces and streets to be green, but this cannot be achieved unless the system is decentralized. The decentralization option relates to several matters considered important, such as planning and decision-making, for example. In practical terms, it can enhance the role of citizens and be a means of resolving local environmental and health concerns accurately, and it may also help improve services (Burton, et al, 2013). The decentralized system often tends to meet the needs of local water use, as treated water helps increase agricultural productivity and is also suitable as an alternative to landscaping and replenishing groundwater resources (Environs Associates, 2018).

There are advantages of systems. On the other hand, there are disadvantages as well. In a centralized water system there is uniformity, and it assures the demand and quality standard of the population. Due to shortages of water resources and other related factors, communities insisted on paying adequate attention to using water. In addition, decentralized water system can spread a high risk of drought in the locality. In a decentralized water system, local water reuse could be used to increase agricultural productivity. Decentralization is a holistic method. It helps the locality to reduce waste of water, helps recycling, and also helps to keep the wastewater collection component at the minimum level. Decentralization method help to reduce the cost by 60% as com-pared to centralized method of water management, thus helping in obtaining sustain-ability and improving environmental health.

## 5. Conclusion

This study evaluated a wastewater decentralized treatment system in Khartoum Locality, focusing on stabilization ponds and MPR technologies. The decentralized stations were found most suitable for urban liquid waste management. The study used wastewater engineering calculations, BioWin simulations, and Excel analysis to evaluate sanitation and wastewater treatment development. The study highlights the importance of considering other factors like sludge management, transportation, effluent discharge, and economic costs for installation, operation, and maintenance. The study emphasizes the need for expert and government opinions in wastewater treatment selection.

The current study has discussed in detail the decentralization method of water management, its benefits and disadvantages. Decentralization method help to improve environmental health, agricultural productivity, reduce cost and help in obtaining sustainability. Due to drought risk, the decentralization method of water management is attracting the attention of researchers and practitioners. Reuse of water not only reduces the cost but also decreases the demand for chemical fertilizers for the agricultural sector. Treated water also helps in the reduction of water crises such as wastewater pollution and lack of water in Khartoum locality, Sudan. Decentralization method would improve water management system and reuse of water help to preserve the natural environment and economic development of the country.

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