Chapter 1- Introduction

Coronaviruses (CoV) are a class of genetically diverse RNA viruses found in a wide range of host species including mammals and birds. (Sun, et al., 2020) Many of them are well known for causing respiratory and intestinal tract infections in both human beings and in animals (Drosten, et al., 2003; Arabi, et al., 2017; Resta, et al., 1985). The coronaviruses first came to spotlight when cases of atypical pneumonia were reported among people of Guangdong province, China in the year 2003 (Zhong, et al., 2003). This subsequently spread to Hong Kong where the virus was isolated and named (SARS-CoV) and the disease was called severe acute respiratory syndrome (SARS). Further studies found the virus to have originated in bats which later spread to humans via intermediate hosts: the Himalayan palm civets (Himalayan palm civets) or racoon dogs (*Nyctereutes procyonoides*) (Shi and Hu, 2008). Another coronavirus of animal origin that created headlines was the middle east respiratory syndrome coronavirus (MERS-CoV) that was first identified in Saudi Arabia in the year 2012 (Al-Raddadi, et al., 2020). The disease was subsequently detected in 27 other countries with major outbreaks in Saudi Arabia, United Arab Emirates and Republic of Korea. Dromedary camels (Dromedary camels) were the usual reservoirs of MERS-CoV from which zoonotic transmission occurred. The disease had a higher case fatality rate than SARS, but transmission to humans was infrequent (De Wit, et al., 2016).

In December 2019, once again, clusters of pneumonia cases of unknown etiology were reported in Wuhan, China with links to a sea food market (Sun, et al., 2020). A new β-coronavirus was isolated and genome sequencing was done (Guo, et al., 2020). This novel coronavirus was named SARS-CoV-2 and the disease was named COVID-19 by the World Health Organization (Singhal, 2020). Prior to March 2020, the epidemic was largely contained in China and measures were being taken to control it. However, after this time, cases began to abate in China while rising at a considerable rate outside (Liang, et al., 2020). Due to its rapid spread, the disease was declared a pandemic on March 11th 2020 by WHO (Shams, et al., 2020)

Up to now, this disease has affected 220 countries and territories of the world extensively with more than 191 million cases and 4 million deaths to date (Worldometer, 2021). Some countries have been affected more than others, with Europe being among the worst affected

continents. In Asia, around 59 million cases have been reported overall with the highest number of cases from neighboring country, India. Bangladesh has also had a surge of cases with the total number of confirmed cases crossing 1 million (Worldometer, 2021).

Although individuals of all ages are at risk of infection with SARS-CoV-2, incidences of serious infections are higher in people aged 60 and above, and those with co-morbidities. However, with the development to new variants, through random mutations of RNA within the virus, there are variations in virulence and infectiousness of the different strains of SARS-CoV-2. Among most of the affected cases, the major clinical signs and symptoms observed were fever, cough, dyspnea, fatigue and loss of senses such as taste or smell. Apart from these some patients have displayed atypical symptoms such as diarrhea and vomiting (Sun, et al., 2020). A considerable number of patients have developed COVID-19 associated complications comprising of respiratory problems like pneumonia and acute respiratory distress syndrome; cardiovascular complications like myocardial infarctions, heart failure and thromboembolic events; and neurological complications like encephalopathy. Incubation period for the disease was usually around five days but could range from two to fourteen days (Shams, et al., 2020).

The treatment for COVID-19 is still evolving with no specific medication approved as yet (Hossein-Khannazer , et al., 2021). Various classes of drugs such as monoclonal antibodies, steroids, etc. are reserved for severe cases of infection while mild cases are given regular analgesics and antipyretics for symptomatic relief (NIH, 2021). In such circumstances, disease prevention remains the mainstay of controlling the contagion.

At individual level, recommended procedures to prevent the spread of this virus include proper hand washing, covering one's mouth when coughing, social distancing, wearing a face mask in public places or in gatherings, and monitoring as well as self-isolation in case an individual suspect he or she may have become infected (WHO, 2021). However, at state and national levels, steps taken by the appropriate governments varied according to the status of the disease in their respective countries. Most governments and authorities worldwide have responded by implementing travel restrictions, lockdowns, workplace hazard controls, and facility closures (Allain-Dupré, et al., 2020). Several countries have

also upgraded their existing medical infrastructures and health personnel to increase testing capacity and accurately trace contacts of infected persons (Shams, et al., 2020).

Since China was the first country to face this epidemic, steps taken to contain the disease had to be drastic in order to prevent its spread worldwide. A strict lockdown and large-scale public health intervention were initiated where confirmed cases were transferred to hospitals for centralized treatment; while all suspected cases and close contacts were moved to designated venues for isolation and medical observation. These strict policies secluded the source of infection and limited any possibility of alternative transmission routes while preventing cross infection (Chen, et al., 2021). All these measures helped control the infection and to date, the country is still in a phase of ongoing prevention and control with 536 active cases as of July 16th 2021 (Worldometer, 2021). In neighboring countries of China, such as Singapore, after the first confirmed case of Covid-19 was reported on 23rd January 2020, strict border control measures were implemented to prevent importing cases. With community prevention and epidemic control measures the situation was mitigated by April that same year, but an outbreak at dormitories of migrant workers lead to a recurrent surge in the number of cases. Hence, the country implemented blocking measures and quarantined migrant workers to contain the infection. Another neighbor of China, South Korea, had their first confirmed case on 20th January 2020 and this was followed by an emergence of a large number of cases a month later owing to a religious group called Shincheonji that harbored the infection within its members and caused it's spread by avoiding protective measures such as social distancing and use of face masks. To contain the spread of the epidemic, the South Korean government adopted certain measures such as massive screening, drive- through screening points and strict social distancing which ultimately helped contain the infection. Since May 6th 2020, the Korean government relaxed its restrictions and entered a phase of limited control measures. However, a surge of cases has been observed recently with over 1,500 new cases diagnosed on a single day (Worldometer, 2021). In Japan, the government has implemented a series of border control measures to prevent infection spread after a case was diagnosed on 15th January 2020. As transmission rate increased in the next two months a "Basic Policy on COVID-19 Countermeasures" was issued by the Ministry of Health, Labor and Welfare. A nationwide state of emergency was declared on 7th April that was lifted on 25th May.

Nevertheless, the outbreak continued to rebound in the following months with the government taking no serious restrictive measures. Currently 3,400 new cases in one day have been reported. (Worldometer, 2021)

South Asia, being one of the world's most populated and poor regions are more vulnerable to this pandemic than other regions owing to their poor healthcare infrastructure and over burdening of health care workers. (Chalise, 2020) The first case in this region was reported on 24th January and was found in a Nepali student travelling from China. Following this, cases were reported in Sri Lanka and India on 27th and 30th January 2020 respectively. Within one year, the number of cases increased drastically and India was leading in both the number of cases and COVID related deaths. Since Bangladesh shares its borders with India, the future of COVID-19 cases largely depends on the situation in India. Up to now, Bhutan seems to be the only country in South Asia, that has been able to control cases of COVID-19 successfully (Chalise, 2020). All of these South Asian countries had imposed strict lock downs, border controls and curfews to prevent the spread of this virus in densely populated areas (Chalise, 2020). Measures such as public broadcasting, training healthcare workers, and establishing central and local testing laboratories were the initial steps taken to rapidly detect diseases. At the same time schools were closed down to control disease spread among students (Panthee, et al., 2020). Despite this, the disease spread extensively to almost all the territories of the South Asia region. As of now, the total number of confirmed cases are 36.5 million with over three- fourth the cases from India alone.

India, a country that surrounds Bangladesh on three sides, is leading in terms of the number of COVID-19 cases, consisting of over 31 million confirmed cases so far and more than 414 thousand deaths (Worldometer, 2021). This outbreak has challenged the country's economic, medical and public health infrastructure. While researchers and healthcare professionals around the world are looking frantically for an effective treatment regime for COVID-19, India has been combating a rapid surge of cases that threatened to exhaust an already overwhelmed healthcare system creating chaos and instability due to lack of resources to deal with the sudden increase in patients (Thiagarajan, 2021). The highest number of cases have been reported from the state of Maharashtra accounting for over 6 million confirmed cases so far.

In case of Myanmar, another country that shares a border with Bangladesh, data on the situation of COVID-19 is unreliable, owing to the sudden military coup amidst the pandemic. Prior to the coup, hundreds of cases were registered on a daily basis, however, after the coup the registration numbers came down to two digits every day. This verifies that a lot of cases go unregistered due to hampered COVID-19 testing in the country in this chaos (Rocha, et al., 2021). Hence, not much is known about the government strategies adopted here and this uncertainty poses as a threat to Bangladesh where migrants that illegally enter the country might be carriers of the virus.

So far, around the world, over 188 million cases have been confirmed with over 4 million deaths and counting. (WHO, 2021). The highest number of cases has been confirmed in the Americas (74.4 million cases), followed by Europe (57.6 million), South-East Asia (36.5 million), Eastern Mediterranean (11.6 million), Africa (4.5 million) and the Western Pacific (3.9 million) (WHO, 2021).

Bangladesh, like other countries, also have taken steps to address the COVID-19 pandemic. A national preparedness and wellness plan was formulated by the ministry of health and family welfare with three main goals- to control the arrival of virus from abroad, to control the spread of virus within the country and to identify and treat infected persons separately (MOHFW, 2020). Despite adopting multiple measures to contain the disease, timeline of COVID-19 distribution within the country progressed quickly. The first case of COVID-19 was identified on 8th March 2020 and the first death was recorded on 18th March 2020. By this time, the infection spread rapidly in places like Narayanganj, Shibchar, and Mirpur in Dhaka (DGHS, 2021). On 26th March the first general lockdown of the country was implemented. Since then, based on sudden surges in cases, lockdowns have been executed every now and then. As of December 2020, there are thirty dedicated COVID-19 hospitals in the country with nineteen of them in Dhaka alone. New testing centers have also been created with 163 centers currently conducting COVID-19 detection tests (DGHS, 2021). Furthermore, procurement of manpower, telemedicine activities and multiple training activities for healthcare workers have all been provided by the government for proper identification, testing and management of cases. Apart from these, the government initiated public campaigns highlighting the necessity of practicing respiratory and hand hygiene and

use of appropriate personal protective equipment (PPE) such as masks and gloves. In spite of taking so many measures, the number of cases continued to rise due to minimal adoption of these practices by the public at large (Banik, et al., 2020). Hence, Covid-19 has become one of the biggest health concerns in Bangladesh with the highest number of confirmed cases recorded in July 2021 (WHO, 2021).

As of 19th July 2021, a total of 1,117,310 cases have been confirmed among which 18,125 have died. Although cases were initially confined to densely populated urban areas, more and more cases are being found in the rural areas owing to lack of knowledge and practices for disease control. (Rahman, et al., 2021). Treatment for Covid-19 in Bangladesh is based on the guidelines set by DGHS. Here, mild cases are given symptomatic treatment while moderate cases are given in addition anti-thrombolytics (Enoxaparin), antiviral (Remdesivir) and steroids based on their oxygen saturation, duration of illness and comorbidities (DGHS, 2021). In critically ill patients, antibiotics are also added as a prophylaxis to prevent infections. Tocilizumab, is used on certain patients who experience rapid respiratory decompensation due to the disease. Other drugs like Ivermectin, Bevacizumab, Baricitinib; and convalescent plasma therapy can only be given on a clinical trial basis as adequate data on its efficacy is still lacking. While physicians in the country are repurposing different drugs to treat cases of COVID- 19 with no clear remedies for the disease, research institutes, both within the country and abroad in collaboration with biotech companies have already identified strategies to produce effective vaccines using viral proteins (Sattar, 2021).

Up till now, four different types of vaccines have been developed and are at different phases of clinical trials. These are RNA- based vaccines (developed by Moderna, Pfizer/BioNTech), DNA- based vaccines (Inovio Pharmaceuticals), non- replicating viral vector vaccines (Oxford/AstraZeneca, CanSino/Beijing, Gamaleya, Janssen and serum institute of India); and inactivated vaccines (Sinopharm and Sinovac). Seven of these vaccines are currently approved for use in Bangladesh. These are the two RNA- based vaccines, the two inactivated vaccines and three out of five non-replicating viral vector vaccines namely Sputnik V (Gamaleya), Ad26.COV2.S (Janssen (Johnson & Johnson)) and Covishield (serum institute of India). Bangladesh has also joined the COVID-19

vaccine race with the development of its own vaccine, Bongavax, by Globe Biotech Ltd. In December of 2020, this vaccine received approval for production to start trials within the country (Sattar, 2021).

On 27th January 2021, Bangladesh government initiated the public vaccination program against COVID-19 with priority for first responders such as physicians, nurses and other healthcare workers (Ahamad, et al., 2021). Covishield, also known as ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), was the preparation distributed by the government of Bangladesh for immunization against Covid-19 in the country. It has been distributed to Zillas and Upazillas at different health complexes and people were expected to register online to receive these vaccinations. This vaccine is similar to the Covid-19 vaccine developed by AstraZenca. While trials have been done involving the elderly population, safety and efficacy has not been established through trials in the pediatric population. Hence, the vaccine is not advised for people below 18 years of age. Among the vaccine trials conducted prior to distribution, majority of the patients were white (83.3%) with an average of only 4.4% of Asians within the trial pools (Voysey, et al., 2021). Hence, data on adverse effects from vaccination within these trials could be different from what should be expected in our country and demographic settings.

So far, no study has been found in Bangladesh that discusses about the impact of post vaccine effects following Covid-19 vaccination. While multiple sources have discussed the array of complications affecting people who received vaccination, no in-depth study has been done yet on this topic. Hence, this research study was undertaken to identify, as accurately as possible, the adverse effects following vaccination with Covishield and what are the risk factors associated with severity of these adverse effects.

Rationale

COVID- 19 pandemic has claimed over 4 million lives worldwide (Worldometer, 2021). Since social distancing and personal protective measures such as frequent hand washing and use of face masks and gloves were unable to hinder the transmission of this deadly virus, vaccination has become an only option to limit disease spread. With the introduction of a mass COVID-19 vaccination program nationwide, almost 6 million people received at least one dose of vaccine in Bangladesh (DGHS, 2021). Since there is limited data available on the safety and efficacy of this vaccine, understanding its impact among the general population has become essential, especially within the elderly age group. It is also important to identify any deleterious impact that the vaccine may have on individuals with pre-existing health issues.

Aim of the study

The aim of the study is to better understand the impact of vaccine in population following immunization with Covishield.

Objectives

- To observe the demographic characteristics among COVID vaccinated population.
- To identify the associated adverse effects of vaccinated people.
- To identify the risk factors and their association with becoming positive for Covid-19 before vaccination.

Chapter 2- Literature Review

2.1 Background

Discovered in the 1960s, coronavirus is a species of positive- sense RNA viruses that is classified under the order Nidovirales, family Coronaviridae, and the subfamily Coronavirinae (Yan, et al., 2020). These viruses can be characterized by the appearance of spikes that protrude on their surface and they have the capability to infect specific vertebrates. On the basis of serological and genomic properties, the coronavirinae subfamily is further divided in to four Genuses: Alpha, Beta, Gamma and Delta coronavirus. The betacoronavirus can be additionally split in to four lineages: A, B, C and D. SARS-CoV-2 that has recently been identified has been classified as subgenus Sarbecovirus of the lineage B genus of betacoronavirus (Letko, et al., 2020). Owing to its widespread availability, large genetic diversity and frequent recombination of the different coronavirus species, along with the increased time humans spend with animals, coronaviruses can occasionally mutate to infect human hosts (Zhu, et al., 2020).

From the different coronavirus species identified so far, there are six species that can infect human hosts (also called HCoV). Depending on the lineage of the coronavirus species as well as the immunocompromised nature of the infected human host, the symptoms can vary from mild illness to severe respiratory distress or even death (Fung & Liu, 2019). Although the new coronavirus SARS-CoV-2 was first discovered in a cluster of patients who reported symptoms of pneumonia of unknown cause to local health facilities in Wuhan, China, in early December 2019, the original source of this virus is yet unclear. (Yan, et al., 2020)

Over the past twenty years, other zoonotic and pathogenic coronaviruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have led to regional or global outbreaks. Although not identical, a lot can still be learned from these previous outbreaks; and the knowledge and experience could be used to understand the new coronavirus.

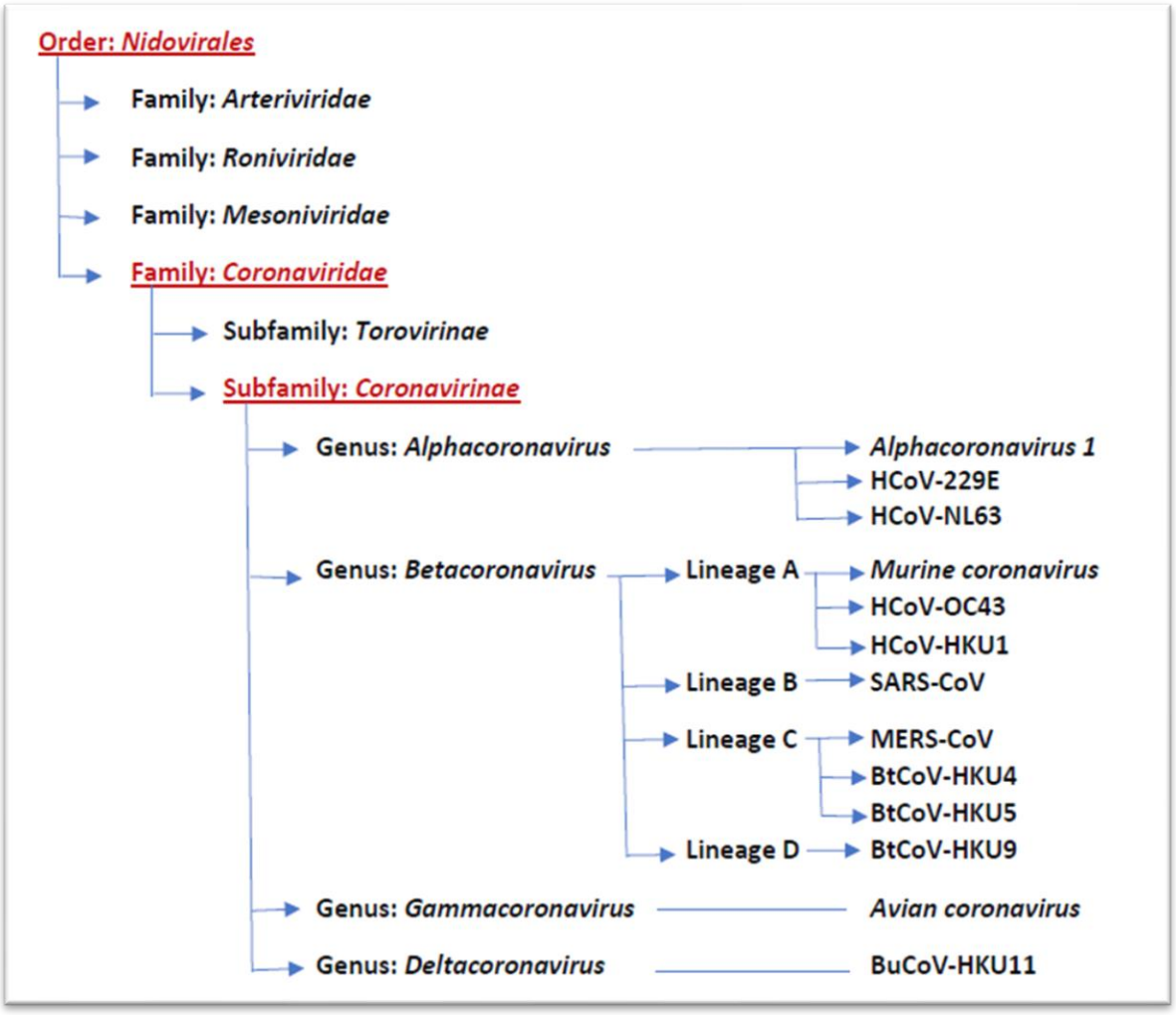


Figure 1: Classification of coronaviruses
Source: *(Fung & Liu, 2019)*

2.2 Evolution of coronavirus

Although SARS-CoV was not the first coronavirus to have infected human beings, its emergence as an outbreak was the first of clinical significance in modern history. In November 2002, the first outbreak of SARS-CoV pneumonia was reported at Guangdong province, China. Empirical therapy using antimicrobials that help treat acute community acquired or atypical pneumonia proved ineffective in handling this disorder. Upon further investigations, it was found that the infecting pathogen was never identified previously and the disorder was named severe acute respiratory syndrome (SARS) (Peiris, et al., 2003). The incubation period was usually 4-6 days after which patients developed flu like

symptoms and pneumonia. By the end of the epidemic in June 2003, SARS led to over 8000 cases worldwide and had a mortality rate of about 9.6%. In an attempt to identify the source of this new virus, samples were taken from animals at live-animal markets in Guangdong province and it was found that masked palm civets and two other species were already infected with SARS-CoV. Since the disease was zoonotic, large-scale culling of masked palm civets were carried out. However, further studies showed that only civets sold at the market had the overt clinical symptoms of SARS-CoV and no wild or domestic civets were infected. This suggested that civets were not likely the primary hosts or natural reservoirs of the virus (Li,2005; Wang, et al.,2006). On the contrary, studies revealed the ability of bats to host several zoonotic viruses while rarely displaying any signs and symptoms (Li, 2005). Furthermore, the increased consumption of bats or bat-based products in southern China raised the suspicion that bats could be the primary hosts for SARS-CoV. Upon collecting serum samples from over 400 bats from nine different species, six genera and three families, it was found that only different species of horseshoe bats from the Rhinolophus genus tested positive for SARS-CoV. Thus, it was concluded that horseshoe bats were the primary hosts of the virus while civets were intermediate hosts and the virus eventually made its way to human hosts (Fung & Liu, 2019).

MERS-CoV was first discovered in Jeddah, Saudi Arabia in the summer of 2012 when the sputum of a patient with acute pneumonia and renal failure showed the presence of an unknown coronavirus. Similar cases were observed earlier in April that same year among healthcare workers in a hospital in Zarqa. Clinical features of these patients resembled SARS where, only a minority of patients experienced mild symptoms while the vast majority experienced a more severe acute respiratory condition (De Groot, et al., 2013). Outbreaks of MERS-CoV reached many countries with over 2000 cases worldwide and a mortality rate of approximately 35% which consisted mostly of the elderly population, children and the immunocompromised (Fung & Liu, 2019). The virus was believed to have been transmitted to humans by dromedary camels which were thought to be intermediate hosts. According to different viral genome analysis, MERS-CoV was suspected to have originated from bats that may have transmitted the virus to camels in the past. Luckily, human-to-human transmission of the virus was not so common as close contact was needed for the virus to pass on to another human host, thus limiting the spread of the virus.

On emergence of cluster of pneumonia cases in Wuhan, China in 2019, suspicion of yet another outbreak was revealed. All confirmed cases of SARS-CoV-2 from 1st to 20th January 2020 that were admitted to Wuhan Jinyintan Hospital were studied and 49% of the subjects had some form of previous exposure to Hunan Seafood Wholesale Market which had live-animals on sale (Chen, et al., 2020). Further study of the viral genome showed that this species of coronavirus was 96.2% identical to a bat coronavirus. Other studies done on genome sequencing of SARS-CoV- 2 also showed similar results suggesting bats to be the primary reservoirs for the virus. However, the intermediate host in passing the virus to humans hosts still remains unclear since several animal species were present at the Wholesale Market (Jiang, et al., 2020).

2.3 SARS-CoV-2 structure

The SARS-CoV-2 is a β- coronavirus which is an enveloped non-segmented and positive-sense RNA virus (Zhu, et al., 2020). They are divided in to four Genera, namely α-, β-, γ-, and δ- CoV. While α- and β- CoV are able to infect mammals, γ-, and δ- CoV tend to infect birds. Formerly, six CoVs have been identified to cause infections in humans among which α-CoVs HCoV-229E and HCoV-NL63; and β-CoVs HCoV-HKU1 and HCoV-OC43 caused mild respiratory symptoms with mild pathogenicity. (Yin & Wunderink, 2018).

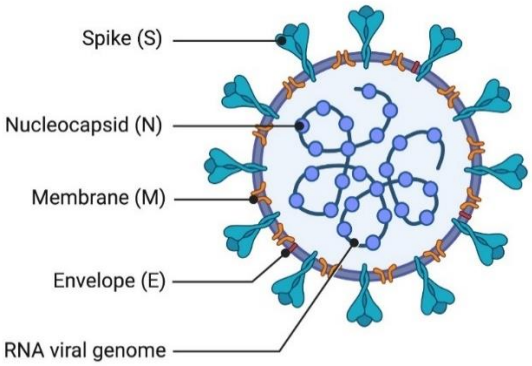


Figure 2- Structure of SARS-CoV-2
Source: (King, et al., 2020)

The coronavirus particles are organized with long RNA polymers tightly packed into the center of the particle, and surrounded by a protective capsid. In coronavirus, these proteins are called nucleocapsid (N). The coronavirus core particle is further surrounded by an outer membrane envelope made of lipids (fats) with proteins inserted. A key set of the proteins in the outer membrane project out from the particle and are known as spike proteins (S). It is these proteins which are recognized by receptor proteins on the host cells which will be infected (King, et al., 2020). From Genome sequencing, it was found that SARS-CoV-2 was 96.2% identical to a bat CoV RaTG13 and 79.5% identical to SARS-CoV.

2.4 Replication of coronavirus

Coronaviruses primarily infects human lung cells through a receptor for an enzyme called Angiotensin Converting Enzyme 2 (ACE2). ACE2 is a member of the family of angiotensin converting enzymes and is found in the lower respiratory tract of humans. As the first step leading to viral infection, the virus spike protein recognizes and binds to the ACE2 receptor. This virus is then fused into the lung cells and the viral RNA is released into the cytoplasm. The viral RNA molecules recruit the host cell apparatus to make thousands of copies of the viral RNA and nucleocapsid, membrane, envelope and spike proteins. These assemble into new virus particles which bud out of the cell surface membrane. The cells release the newly formed viral particles propagating the infection and eventually die.

2.5 Transmission

Human to human transmission can easily occur between close contacts and multiple routes of transmission has been identified. Although the disease primarily spreads by respiratory droplets, respiratory secretions and direct contact, studies have reported the presence of this virus in fecal swabs as well as blood, suggesting that infection could spread in this way also (Zhang, et al., 2020). Since ACE 2 receptors are present in abundance in the lung alveoli as well as the enterocytes of the small intestine (Hamming, et al., 2004), routes of infection as well as disease manifestation can be understood from this.

2.6 Clinical Features

The clinical features of SARS-CoV-2 is highly variable from person to person with asymptomatic cases to acute respiratory distress syndrome and multi-organ failure. From various studies of laboratory confirmed cases, the common clinical manifestations included fever, cough, fatigue, production of sputum, shortness of breath and sore throat. Additionally, some patients may present with gastrointestinal symptoms like diarrhea and vomiting. Elderly patients and patients with comorbidities such as diabetes, hypertension, COPD, cardiovascular diseases, etc. rapidly develop acute respiratory distress syndrome, shock, metabolic acidosis and coagulation dysfunction leading to death (Huang, et al., 2020).

2.6.1 Antibody response against COVID-19

Generally, antibodies to SARS-CoV-2 are not detectable in the very early stages of infection. One study by Liu et al (Liu, et al., 2020) showed that anti-SARS-CoV-2 IgM antibodies were detectable from the 4^{th} day of illness onset which increased over time and peaked at 20 days after which it gradually declined and was markedly reduced after 28 days. Anti-SARS-CoV-2 specific IgG antibodies were detectable from day 7 of illness onset and peaked at approximately 25 days of illness onset and the levels were still maintained high 4 weeks later. In the early stages of infection, no significant difference was observed in serum IgG levels between mild and severe cases, but after 15 days of disease onset, both IgM and IgG levels were vigorously raised in cases of severe illness. Furthermore, the timing in developing IgM and IgG antibodies varied greatly among patients and this could be associated with age and comorbidities of the patient.

2.6.2 Cytokine response against COVID-19

The immune system has an attractive mechanism capable of responding to a variety of pathogens. For any normal antiviral immune response, activation of the inflammatory pathways of the immune system is necessary, however, exaggeration of the host's immune system can lead to severe disease if this remains uncontrolled (Braciale & Hahn, 2013). Cytokines are produced by numerous immune cells including the macrophages, dendritic cells, natural killer cells and the T and B lymphocytes. During an innate immune response

to any viral infection, there are pattern recognition receptors (PRRs) that recognize the different molecular structures distinctive to the invading virus. These structures are referred to as pathogen associated molecular patterns (PAMPs). When PAMPs bind to PRRs an inflammatory response is triggered against the invading virus. This results in activation of various signaling pathways and later transcription factors which induce gene expression responsible for production of several products involved in the host's immune response to the virus. Among these are the genes encoding several pro-inflammatory cytokines. The major transcription factors activated by PRRs are activation protein 1, nuclear factor kB and interferon response factors three and seven. These transcription factors induce the expression of genes that encode the inflammatory cytokines, chemokines and adhesion molecules. This sequence of events results in the recruitment of leukocytes and plasma proteins to the site of infection where they perform many effector functions that help to combat the triggering infection (Thompson, et al., 2011).

Three important pro-inflammatory cytokines of the innate immune response are IL-1, TNF-α, and IL-6. These cytokines are produced by mast cells, tissue macrophages, endothelial cells, and epithelial cells during an innate immune response. When there is an acute increase in circulating levels of different pro-inflammatory cytokines such as IL-6, IL-1, TNF- α, and interferon, it causes a sudden influx of various immune cells such as macrophages, neutrophils, and T cells in to the infection site. This is called “cytokine storm” and it has a destructive effect on human tissue due to damage of vascular barrier, capillary damage, diffuse alveolar damage, multiorgan failure and finally death. Lung injury is one consequence of the cytokine storm that can easily progress into acute respiratory distress syndrome (ARDS) (Shimizu, 2019). This leads to low oxygen saturation level and hence is a major cause of death in COVID-19 patients.

Multiple studies suggest that some patients with COVID-19 suffer from a cytokine storm (CS). One study analyzed the cytokine levels of 41 COVID-19 confirmed cases with pneumonia and found elevated levels of IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α, and VEGF in these patients as compared to healthy adults (Huang, et al., 2020). One specific marker that was significantly raised in severe cases of COVID-19 was IL-6. Multiples studies showed this

specific finding where raised IL-6 levels were significantly higher in cases who died (Ruan, et al., 2020) or when comparing between mild and severe cases (Chen, et al., 2020).

CS has been reported in many viral infections including the previous two coronavirus infections-SARS and MERS. Both pro-inflammatory and anti-inflammatory cytokines are raised in the serum of patients with CS. Hence in COVID-19 patients, along with antiviral therapy, anti-inflammatory therapies that reduce cytokine responses are necessary. (Ragab, et al., 2020).

2.6.3 Cellular response against COVID-19

Cellular response of COVID-19 varies from patient to patient. In patients with mild symptoms and patients with severe disease who have recovered exhibit a normal immune response to eliminate the virus. However, patients with fatal severe COVID-19 went through three stages: normal or hypofunction, hyperactivation and then anergy. Ultimately, these patients are unable to resist the viral infection and they die (Zhou & Ye, 2021).

In the early stages of COVID-19, the total number of white blood cells in peripheral blood is either normal or decreased (National Health Commission of the People's Republic of China, 2020). T and B lymphocytes are cells that are important indicators for detecting immune function. These T lymphocytes are further classified into two important subsets: CD3+ CD4+ T lymphocytes and CD3+ CD8+ T lymphocytes. CD4+ T cells can differentiate into a range of helper and effector cell types, as well as have the ability to indicate B cells, assist CD8+ T cells, have direct antiviral activity, recruit innate cells and promote tissue repair. On the other hand, CD8+ T cells can kill infected cells and affect the activation of the immune response. As another important component, B lymphocytes play a role in humoral immunity by secreting antibodies. In normal viral infections, the lymphocyte counts increase in response to the infection. However, contrary to this, in Covid-19 infections, the lymphocyte counts decrease with increasing severity of the disease (Schulte-Schrepping, et al., 2020). The number of T lymphocytes in sever patients were lower than in mild patients, and much lower in deceased patients. Even the B lymphocytes are decreased with patients with severe illness having lower counts than those

with mild illness. Nevertheless, B lymphocyte counts were within the normal range (Zhou & Ye, 2021).

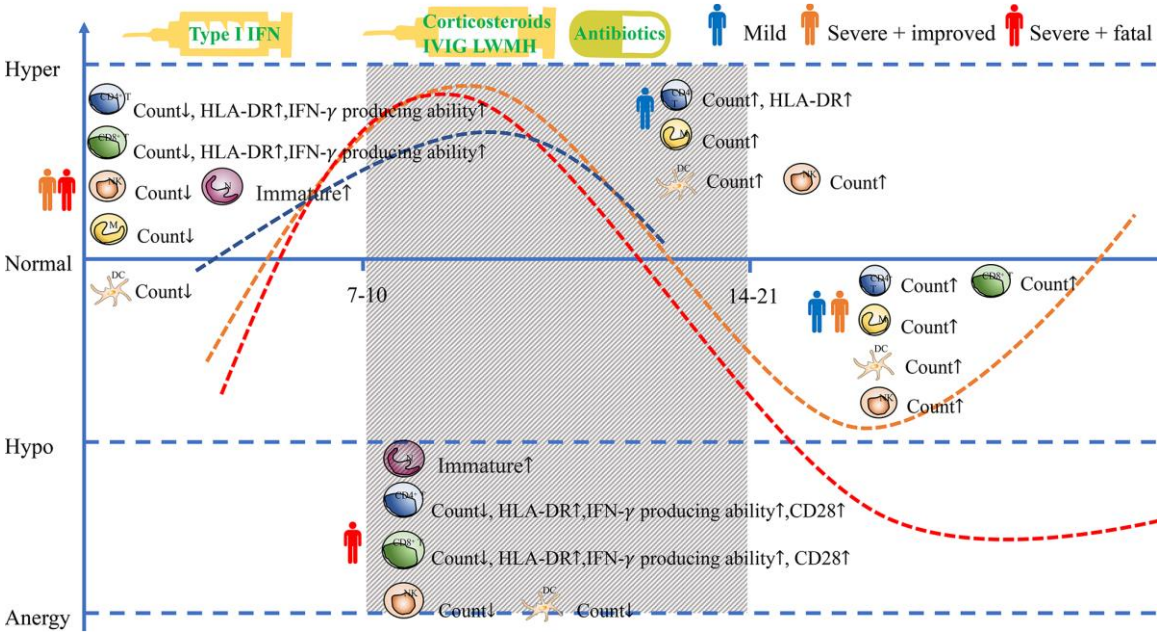


Figure 3: Cellular immune response to SARS-CoV-2

(Source-Zhou and Ye 2021)

Due to the initial local respiratory SARS-CoV-2 infection, the circulating innate immune cells in the blood, including natural killer cells, monocytes, neutrophils and dendritic cells changes. The neutrophils are increased in circulation of severe COVID-19 patients, while the dendritic cells the body's most potent full-time antigen-presenting cells (APCs), decreases with severity of disease.

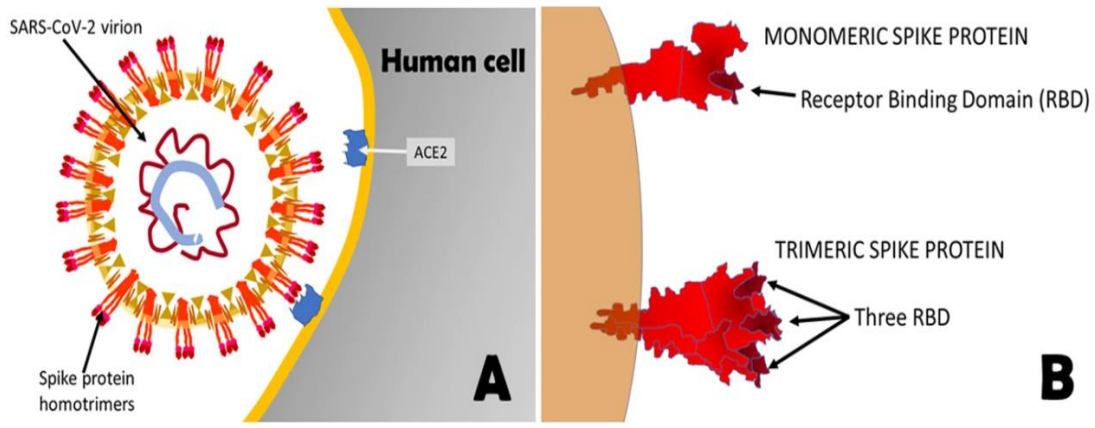


Figure 4: Spike as a target for vaccine development

Source: (Forni & Mantovani, 2021)

2.7 Laboratory diagnosis

Similar to other viral infections, appropriate collection of specimens is key to proper diagnosis of the disease. Acceptable specimens include upper respiratory tract specimens, lower respiratory tract specimens, stool specimens, whole blood specimens, and serum specimens, with respiratory tract specimens being the most frequent. There are many different types of tests that can be used to diagnose COVID-19. The testing of SARS-CoV-2 is grouped into molecular testing and serology testing.

The molecular testing includes nucleic acid amplification test (NAAT) such as real-time reverse-transcription polymerase chain reaction (rRT-PCR). The unique sequence RNA of the virus including nucleocapsid (N), envelope (E), spike protein (S), and RNA-dependent RNA-polymerase (RdRP) genes are targeted to analyze using rRT-PCR. The nucleotide sequence of the viral RNA molecules is not found in human DNA or RNA sequences. The test for the presence of the virus, thus, tests for the presence of the viral RNA sequences in tissue samples. This test requires adequate supplies of two enzymes and the primers, specialized instruments for running the reaction at elevated temperatures, and trained personnel.

- **Antibody (Serology) Test**: A more traditional test for virus infection is the presence of antibodies that bind to the virus. Such tests identify individuals who are now healthy but have previously been infected. Antibody tests require a small drop of blood and are much more rapid than the current nucleotide sequencing tests. It detects antibodies that are made by the immune system in response to a threat, such as a specific virus. It is not used to diagnose active infection. The serology testing of COVID-19 is not targeting the virus itself but the antibodies such as immunoglobulin M (IgM) and immunoglobulin G (IgG) induced following viral infection. These immunoglobulins are serological testing markers after the patient has early (3–6 days after exposure to the virus, IgM) and late virus infections (after 8 days, IgG) response respectively.

The absence and/or poor implementation of both RT-PCR and antibody-based tests early in the outbreak is the main cause of failure to control the outbreak particularly after the experiences of the SARS and MERS viruses.

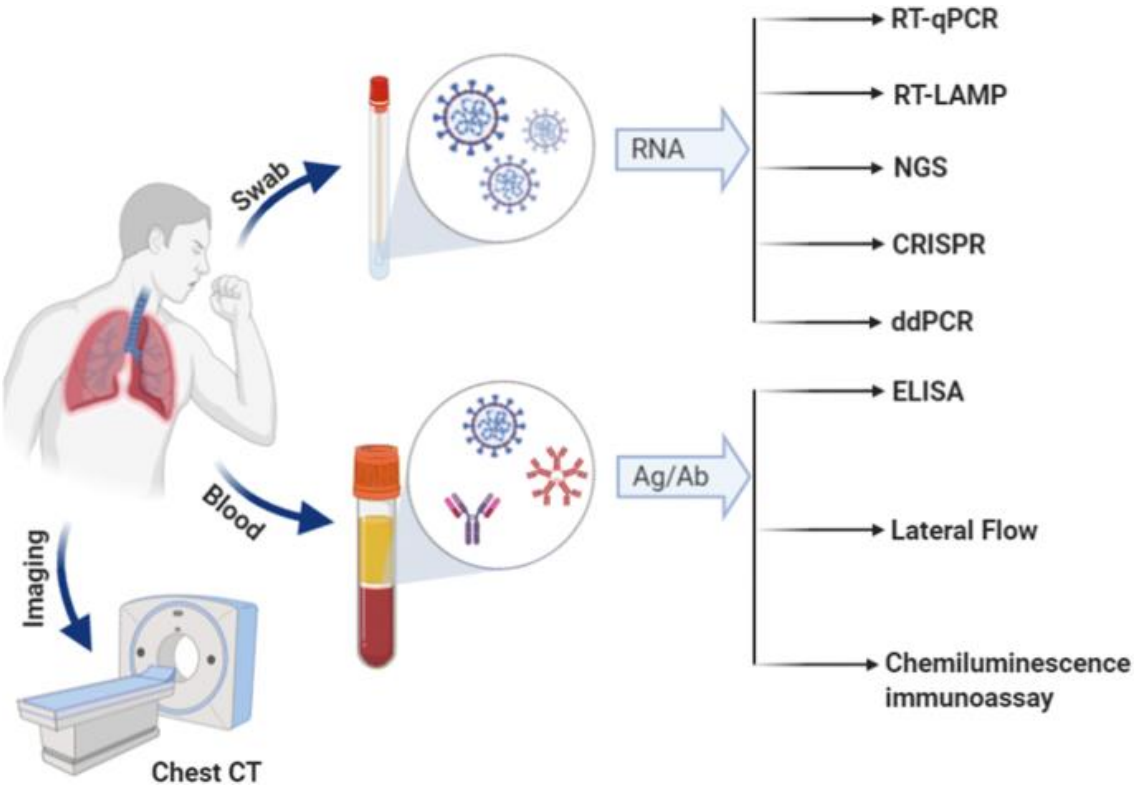


Figure 5: Various analytical methods available for SARS-CoV-2 detection

Source- (Rai, et al., 2021)

Currently, the routine clinical diagnosis of Covid-19 is based primarily on epidemiological history, clinical manifestations, and is confirmed by various laboratory methods such as CT scan, nucleic acid amplification test amplification test (NAAT), and serological techniques. For early screening and diagnosis, specimens like nasopharyngeal swabs, oropharyngeal swabs, bronchoalveolar lavage fluid, bronchial aspirate, sputum, and blood are generally recommended.

2.8 Disease burden

Worldwide, a total of 219 countries and territories have reported confirmed cases of Covid-19 with a death toll of over 3 million. The highest number of cases were found in the United States, followed by India and Brazil.

In Bangladesh, with the rising number of cases and deaths from Covid-19 lies another fear of unemployment, and deepening poverty due to mandatory lockdowns and decline in national and international demands for manufactured goods such as the garments factories (Mohiuddin, 2020). Due to an overwhelming number of cases, and lack of adequate ICUs, hospitals find it hard to meet patient demands and accommodate severely ill patients. Added to this is the attitude and practices of the general population regarding disease awareness and spread. Proper measures are not taken by many and over-crowding despite several warnings and strict regulations continue to exist. Hence, community transmission has become unavoidable. Again, infection of healthcare workers who are frontline fighters for this disease has worsened the situation to such an extent that there are not enough workers to deal with the excessive burden of diseases. One ray of hope that could stop this deadly disease is the emergence of effective vaccines.

2.9 Prevention

Coronavirus particles are rapidly inactivated – killed – by exposure to 70% ethanol or 90% isopropanol (rubbing alcohol), hydrogen peroxide solutions, hypochlorite bleach, soaps and detergents, as well as by UV light and the high temperatures of cooking (King, et al., 2020). Hence, preventive measures include physical distancing, use of masks to prevent

droplet infections, constant washing of hands with soap and water to prevent transmission and use of personal protective equipment (PPE) by health care workers. Another method of prevention is the use of vaccinations to immunize people against the disease.

2.9.1 Vaccination

The appearance of various strains of COVID-19 and its impact on global health has made the development of a safe and effective vaccine vital for this new lethal disease. So far, three main types of vaccines are in use for this disease- inactivated whole-virus vaccines, adenoviral vector vaccines and messenger RNA- based vaccines. (Bogdanov, et al., 2021)

2.10 Covishield vaccine

Covishield is the vaccine currently approved for use in Bangladesh to prevent the spread of COVID- 19. Each dose of 0.5ml of the ChAdOx1 nCov-19 Corona Virus Vaccine (Recombinant) consists of 5×10^{10} virus particles. This product contains genetically modified organisms. The vaccine solution is colorless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6. Covishield is indicated for active immunization of individuals $\geq$ 18 years of age for the prevention of coronavirus disease 2019.

Dosage

The vaccination course consists of two separate doses of 0.5ml each. The second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for the administration of the second dose up to 12 weeks after the first dose from studies overseas.

Mechanism of Action

Covishield is a monovalent vaccine composed of a single recombinant, replication deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein for SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Clinical efficacy

According to four randomized control trials conducted in UK, South Africa and Brazil (Voysey, et al., 2021); no Covid- 19 related hospital admissions occurred in recipients of the vaccine. Vaccine efficacy from 22 days after the 1st dose was 73% (95% CI:48.79-85.76). The efficacy was similar for people with other co-morbidities (Knoll & Wonodi, 2021).

Immunogenicity

Following vaccination with ChAdOx1 nCov-19 Corona Virus Vaccine in participants who were seronegative at baseline, seroconversion (as measured by ≥ 4-fold increase in baseline from S-binding antibodies) was demonstrated in ≥ 98% of participants at 28 days after the first dose and >99% at 28 days after the second dose. Higher S-binding antibodies were observed with increasing dose intervals.

Administration of vaccine

A dose of 0.5 ml of vaccine is administered intramuscularly using separate sterile needle and syringes for each individual. This vaccine does not contain any preservatives, and once opened, should be used as soon as practically possible and within 6 hours if kept between $+2^0$ C and $+25^0$C. To facilitate the traceability of vaccine, the name and number of the administered product is recorded for each recipient.

Adverse drug reactions

According to the safety profile from overseas studies in UK, South Africa and Brazil (Voysey, et al., 2021); majority of the participants were between 18 to 64 years of age and were white. The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse effects were mild to moderate in severity and usually resolved within a few days of vaccination. The adverse reactions were generally milder and reported less frequently in older adults (≥ 65 years old). If required, anti-analgesics and anti-pyrectics could be used to provide symptomatic relief from vaccine reactions.

2.11. Pfizer-BioNTech COVID-19 Vaccine

This is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes the prefusion spike glycoprotein of SARS-CoV-2. It is recommended for use in people aged 16 years and above. The Pfizer vaccine has to be shipped in specially-designed, temperature-controlled thermal shippers that keep conditions around -70 degrees Celsius (-94 degrees Fahrenheit). It can be stored in those conditions for up to 10 days. From there, it needs to be stored in "ultra-low temperature freezers" for up to six months. The vaccine can also be stored in refrigeration units that are "commonly available in hospitals" at temperatures between 36 to 46 degrees Fahrenheit for five days.

Dosage

At least two doses of Pfizer-BioNTech COVID-19 (0.3 mL each) need to be administered intramuscularly for protection against COVID-19. The second dose is given at least three weeks after the first dose. (Oliver, et al., 2020). It provides immunogenicity for at least 119 days after the first vaccination and is 95% effective in preventing the SARS-COV-2 infection. (Meo, et al., 2021)

Mechanism of Action

It is an mRNA (BNT162b2) vaccine. This vaccine is comprised of a nucleoside modified messenger RNA (mod RNA) encoding an optimized viral full-length spike (S) glycoprotein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The S glycoprotein is the target of virus neutralizing antibodies. The messenger RNA (mRNA) is encapsulated in lipid nanoparticles (LNPs) which enables entry into host cells by protecting the naked mRNA from RNases after injection and enhancing its uptake into cells surrounding the injection site by endocytosis. Thus, formulation in LNPs enables expression of the S protein, and elicitation of both antibody and cellular immune responses. mRNA is the connecting step between the protein-encoding deoxyribonucleic acid (DNA) and protein - or antigen - production in the cellular cytoplasm by ribosomes. Once the mRNA used in a vaccine is inside the body’s cells, the cells use their genetic machinery to translate the genetic information and produce the antigens encoded by the mRNA vaccine. The antigens

are then displayed on the cell surface, where they are recognized by the immune system which generates a response, including the production of antibodies against the antigen.

Clinical efficacy

The vaccine was 95.0% effective (95% confidence interval = 90.3%–97.6%) in preventing symptomatic lab-confirmed COVID-19 in people without any evidence of previous Covid-19 infection. Consistent high efficacy (≥92%) was observed across age, sex, race, and ethnicity categories and among persons with underlying medical conditions. On a secondary analysis, efficacy was found to be higher even among participants with or without any evidence of previous SARS-CoV-2 infection.

Contraindications

This vaccine is contraindicated in people with a history of hypersensitivity to vaccines. This vaccine should be postponed in people with confirmed or suspected infection with COVID-19. It should be avoided in acutely ill individuals, people who are immunocompromised, or people who have received any other non-COVID vaccine within the past 14 days. Pregnant and breast-feeding individuals should not be given the vaccine due to lack of appropriate data from clinical trials.

Administration of vaccine

Like all other COVID-19 vaccines, it is administered in the upper arm (deltoid muscle) and will need two doses given 21 days apart.

Adverse drug reactions

Among vaccine recipients, immediate adverse reactions at the site of injection within 7 days were frequent and mostly mild to moderate. Systemic adverse reactions were more commonly reported after the second dose than after the first dose and were found to be more frequent and severe in persons aged 18–55 years than in those over 55 years of age. The median onset was 1–2 days after vaccine receipt and it usually resolved in about one day. Severe local and systemic adverse reactions that interfered with daily activity were common with vaccination. Among vaccine recipients, the most common symptoms were

fatigue (4.2%), headache (2.4%), muscle pain (1.8%), chills (1.7%), and injection site pain (1.4%). Severe reactions were more commonly reported after the second dose than after the first dose and were less prevalent in older than in younger participants.

2.12. Moderna Vaccine

This is another mRNA vaccine developed after the Pfizer-BioNTech vaccine with a lot of similarities in composition. However, it has difference in storage properties, where this vaccine can be shipped at -20 degrees Celsius (-4 degrees Fahrenheit) and can stay stable in refrigeration units between 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) for 30 days. This makes it easier to store and transport. The vaccine will stay stable at -20 degrees Celsius for up to six months and at room temperature for up to 12 hours.

Dosage

Two doses of 0.5ml vaccine are given 28 days apart. The vaccine is recommended for use in people aged 18 years and above.

Mechanism of Action

It is an mRNA (mRNA-1273) vaccine. This vaccine works in a similar way as Pfizer-BioNTech vaccine where vaccines use pieces of the encoded proteins (mRNA) to ignite an immune response in the body. The RNA provides instructions to the body's cells to produce antigens. Those cells then present the antigens to the body's immune system, prompting T-cell and antibody responses to fight the disease. in short, the vaccine elicits an immune response to the S antigen, which protects against COVID-19. The antibodies are specific to the SARS-CoV-2 virus, to protect against a future infection (Dong, et al., 2020; Anderson, et al., 2020).

Clinical efficacy

The vaccine immunogenicity for at least 119 days after the first vaccination and 90 days after the second vaccination (Widge, et al., 2021). It is 94.5% effective in preventing the SARS-CoV-2 infection.

Contraindications

Contraindicated in people with history of hypersensitivity to vaccines or any of their products, people below 18 years of age, pregnant women, breast-feeding women, and immunocompromised individuals.

Administration of vaccine

This vaccine is also administered intramuscularly in the deltoid muscle with a gap of 28 days between vaccinations.

Adverse drug reactions

Taking this vaccine can result in mild adverse effects after the first or second doses, including pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and can also rarely cause anaphylactic shock. Moreover, facial swelling and Bell's palsy has also been reported. (Vaccine, 2021)The adverse effects are comparatively more common with this vaccine than with the Pfizer vaccine. The symptoms are more severe after the second dose than after the first one.

2.13. Janssen (Johnson & Johnson) Vaccine

The Janssen vaccine is based on using a double stranded DNA within an adenovirus type 26 for access in to body cells elicit an immune response against the coronavirus spike protein. This is similar to the vaccine developed by Astra- Zeneca where Chimpanzee adenovirus was used. Since DNA is not as fragile as RNA, and the adenovirus's tough protein coat helps protect the genetic material inside, the Johnson & Johnson vaccine can be refrigerated for up to three months at 36–46°F (2–8°C). However, once a vaccine vial is opened, the vaccine needs to be kept between 2°C and 8°C (36°F and 46°F) for up to 6 hours or at room temperature (up to 25°C or 77°F) for 2 hours.

Dosage

A single dose of 0.5ml vaccine is given to adults of 18 years and above.

Mechanism of Action

This vaccine uses existing technology that involves the adenovirus (Type 26) which commonly causes respiratory infections. After the vaccine is injected into a person's arm, the adenoviruses bump into cells and latch onto proteins on their surface where the cell then engulfs the virus in a bubble and pulls it inside. Once inside, the adenovirus escapes from the bubble and travels to the nucleus where the cell's DNA is stored. The adenovirus pushes its DNA into the nucleus. The adenovirus is engineered so it can't make copies of itself, but the gene for the coronavirus spike protein can be read by the cell and copied into a molecule called messenger RNA. The mRNA leaves the nucleus, and the cell's molecules read its sequence and begin assembling spike proteins. Some of the spike proteins produced by the cell form spikes that migrate to its surface and stick out their tips. These protruding spikes and spike protein fragments can then be recognized by the immune system.

The adenovirus also provokes the immune system by sending out warning signals to activate immune cells nearby. By raising this alarm, this vaccine causes the immune system to react more strongly to the spike proteins. When a vaccinated cell dies, the debris contains spike proteins and protein fragments that can then be taken up by a type of immune cell called an antigen-presenting cell. The cell presents fragments of the spike protein on its surface. When other cells called helper T cells detect these fragments, the helper T cells can raise the alarm and help provoke other immune cells to fight the infection. Other immune cells, called B cells, may bump into the coronavirus spikes on the surface of vaccinated cells, or free-floating spike protein fragments. A few of the B cells may be able to lock onto the spike proteins. If these B cells are then activated by helper T cells, they will start to proliferate and release antibodies that target the spike protein. The antibodies can latch onto coronavirus spikes, mark the virus for destruction and prevent infection by blocking the spikes from attaching to other cells. The antigen-presenting cells can also activate another type of immune cell called a killer T cell to seek out and destroy any coronavirus infected cells that display the spike protein fragments on their surfaces.

Clinical efficacy

Initially, the Johnson & Johnson vaccine was shown to produce antibodies against SARS-CoV-2 in 90% of people who received it after the first dose. The number of antibodies was greater for those who received 2 doses of the vaccine. Data suggest that 1 dose of vaccine was 66% effective in preventing moderate to severe COVID-19 and 100% effective in preventing COVID-19–related hospitalization and death (Mahase, 2021).

Contraindications

Any person with a severe allergic reaction to any ingredient of the vaccine composition should avoid this vaccine. It should not be given in people below 18 years of age.

Administration of vaccine

The vaccine is given intramuscularly in the deltoid muscle.

Adverse drug reactions

In the studies of this vaccine, no one developed a severe allergic reaction, and side effects of the vaccine were similar to those of other vaccines. In clinical trials, side effects were common within 7 days of getting vaccinated but were mostly mild to moderate. Side effects were more common in people 18–59 years old compared to people 60 years and older. The vaccine did not appear to cause any excess serious complications. (Livingston, et al., 2021) However, recently reports of a few cases of blood clots between six to thirteen days post vaccination have prompted authorities in some countries to stop administering this vaccine. It occurs at a rate of about 7 per 1 million vaccinated women between 18 and 49 years old. For women 50 years and older and men of all ages, this adverse event is even more rare.

2.14 Mixing of different vaccines

Since the pandemic began, countries of the world have been struggling to obtain adequate vaccines for their people. However, as expected in any pandemic, the supply of vaccines cannot meet the demands of the general population and hence, mixing of vaccines is considered as an option when trying to ensure proper vaccination for everyone. Except for the Janssen (Jhonson & Jhonson's) vaccine all other vaccines require two doses to warrant

adequate immunity against the virus. Since these vaccines need to be given twice with an interval of at least four weeks, Scarcity of vaccines to provide second doses were observed. (Parkins, 2021) Hence, some countries have considered mixing doses to make sure every person receives two doses of vaccine. In fact, some countries in Europe such as Germany and France recommended the use of an mRNA vaccine as the follow up dose in people below 55 and 60 years of age respectively to boost their immune system. Other countries like Norway and the UK are awaiting results of clinical trials to make this decision. In the UK, concern about complications following the Astra Zeneca shot has already discouraged many from taking a follow up shot. If vaccine mixing is proved to be safe, then such individuals can take an alternate vaccine for their second dose hence avoiding unfavorable vaccine adverse effects.

2.15 COVID vaccine for children

Recently trials have begun in the United States to vaccinate children below 12 years of age against Covid-19. Their aim is to observe how safe and effective these vaccines are for this age group. Under normal circumstances, children rarely develop Covid-19 infection with very little chances of death if they fall ill. However, some of these children who show mild infection could develop a multisystem inflammatory syndrome that is life threatening. In order to prevent such conditions attempts are being made to ensure vaccine safety in this age group. Currently all adults and adolescents are eligible for vaccination. But with changing variants of the virus, and developing herd immunity among adults, children might become contributors in spreading the disease if proper preventive measures are not confirmed for them. The trials are similar to adult trials and initially older kids will be used for dose adjustment of the vaccine so that maximum immunity is obtained with minimum adverse effects from the vaccine. As soon as an ideal dose is finalized, randomized control trials will enroll children of varying ages who will receive two doses of the vaccine or a placebo and their outcomes will be observed through immune markers in blood since very few children develop symptomatic infections.

Since the immune system of children has not been exposed to many pathogens, a strong response to vaccines is expected. This was proved by earlier trial results using the Pfizer-BioNTech vaccine where children between 12-15 years of age developed a higher level of

viral antibodies as compare to trials using 16–25-year-old. However, one disadvantage of this extremely potent immune system in kids is that it increases the chances of adverse effects following vaccinations. Further plans involve conducting trials on under-five children and attempting to incorporate this vaccine in to their immunization schedule. (Callaway, 2021)

2.16 Thrombotic complications of COVID-19 vaccination

Covid-19 infections have commonly been associated with thrombotic complications either from the direct viral attacks on the endothelium cells, or from the 'cytokine storm' due to the host's immune response. Studies have shown both cerebral venous sinus thrombosis and splanchnic vein thrombosis to be high, particularly among critically ill patients thus making intensive care unit admissions inevitable. In fact, one recent study showed a reasonable percentage of patients suffering from pulmonary embolism further highlighting the risks of thromboembolism in these settings. With the introduction of vaccination against the disease, it was presumed that the incidences of covid-19 infections would fall and so would the incidences of thromboembolic events overall. However, a different scenario was observed, where patients receiving specifically the ChAdOx1 nCov-19 vaccine such as Astra-Zeneca and Covishield reported incidences of thromboembolic events often associated with thrombocytopenia post vaccination. Following this discovery, the vaccine was put on hold for a few days only to be resumed later on since the benefits of vaccination were reported to outweigh the risks of thromboembolic events.

The cause of these events was reported to be due to immune thrombotic thrombocytopenia that were mediated by platelet-activating antibodies against platelet factor 4. (Greinacher, et al., 2021). Studies conducted in Norway (Schultz, et al., 2021) and the United Kingdom (Scully, et al., 2021) yielded similar results and more than 40% of the patients died due to superimposed hemorrhage or ischemic brain injury. This post vaccination clinical condition has been named 'vaccine-induced immune thrombotic thrombocytopenia (VITT)'. Further studies involving vaccines other than ChAdOx1 nCoV-19 have also shown rare incidences of similar complications (Smadja, et al., 2021). although it is unclear as to which of these vaccines show a higher incidence of VITT, it has been agreed that vaccine use should not be halted since it is lifesaving.

2.17 Neurological complications of COVID-19 vaccines

Since the introduction of vaccination against COVID-19, numerous complications were reported. Among them were cases of neurological complications such as Guillain-Barre Syndrome (Waheed, et al., 2021), vaccination associated myelitis (Malhotra, et al., 2021), Bell's palsy (Alfishawy, et al., 2021), and other anaphylactic reactions. Concerns for these reactions intensified after cases of transverse myelitis had been reported with the use of AstraZeneca vaccine (Allen, et al., 2020). Similarly, few cases of Bell's palsy were observed among recipients of mRNA vaccines such as Moderna and Pfizer/BioNTech. Among recipients of the DNA based vaccine Johnson & Johnson's, there were very rare reports of Guillain-Barre Syndrome (GBS). However, none of the studies could confirm a significant difference in case incidences between and vaccinated and non-vaccinated people. In other words, the incidences of such diseases were similar among people who did not take any vaccines as compared to people who took vaccines. In the United States, adverse effects of vaccination can be reported by healthcare workers in Vaccine Adverse Event Reporting System (VAERS) via the Center for Disease Control (CDC). So far, the most common neurological symptoms reported were headache, dizziness, pain, myalgia, muscle spasms and paresthesia that are expected to occur as acute and transient effects of vaccination. Also reported were cases of facial palsy, stroke, transverse myelitis and encephalomyelitis, in descending order of frequency. However, a causal link could not be established between vaccination and development of neurological adverse events (Goss, et al., 2021).

Although no neurological condition is a contraindication for getting vaccinated against COVID-19, patients with such conditions receiving immunosuppression therapy have some special considerations. Since some of these medications can weaken the immune response to vaccine antigens, timing of vaccination is crucial for them. For patients taking disease modifying therapy for multiple sclerosis, vaccination should be timed for before the start of therapy or near the end of a treatment cycle. If patients develop GBS within 4-6 weeks after the first vaccine, future vaccinations should be avoided.

2.18 Prevalence of post vaccination adverse effects among healthcare workers

Prevalence of adverse effects following vaccination with COVID-19 varied among different healthcare workers in different settings. In Germany, the mRNA-based Pfizer-BioNTech and Moderna vaccines were given to healthcare workers where over 88% of healthcare workers complained of at least one adverse effect (Klugar, et al., 2021). Similarly, in the Czech Republic symptoms such as pain on injection site fatigue, headache muscle pains and chills were the most commonly reported adverse effects. The prevalence of at least one adverse effect in this study was 89.8%, close to the previous study (Riad, et al., 2021). In south Asian countries, Covishield was used among healthcare workers. Here the prevalence of adverse effects was comparatively less that that reported for mRNA-based vaccines. One study on healthcare workers in India, reported 57% non-serious AEFI after the first dose and 14.1% after the second dose (Kamal, et al., 2021). In another study from Nepal, about 80.9% complained of adverse effects following immunization with pain at the injection site being the most common. In Bangladesh, so far, no such study has been done as yet. So, the prevalence of adverse effects following immunization is yet unknown.

2.19 Acceptability of COVID-19 vaccination among healthcare workers

Vaccine hesitancy (VH) refers to the "delay in acceptance or refusal of vaccines despite availability of vaccine services". It is an emerging public health challenge nurtured by misrepresentation of facts related to vaccines effectiveness and safety (Riad, et al., 2021). Since healthcare workers are usually exposed to various infections and usually play a role in nosocomial spread of infection, they become an important target group for vaccination. In one study 27% of Health care workers were either hesitant or against taking a vaccine for COVID-19. Among them the most hesitant were auxiliary nurses and technicians. In contrast, medical officers and nurses were more likely to accept vaccination (Paris, et al., 2021). Another study showed a vaccination acceptance rate of 91.7% among healthcare workers with the below 20 years age group showing the lowest rate of acceptance (Holzmann-Littig, et al., 2021). Major causes of hesitancy were lack of trust in authorities and pharmaceutical companies. One attitude that was common to most vaccine hesitant healthcare workers was that they obtained information about COVID-19 vaccines from online video platforms and messenger services. Another reason sited was a history of

previous adverse effects to other vaccines and knowing little about the long-term adverse effects of the newly developed COVID-19 vaccine.

2.20 Current situation of vaccination

As of 2nd September 2021, around 35.1% of the world population has received at least one dose of COVID-19 vaccine. Already 5.38 billion doses have been administered globally among which 2.15 billion doses have been administered in Asia alone. On a daily basis, 29.58 million doses being administered worldwide. However, in underdeveloped nations only 1% of the population has received at least one dose of vaccine (Ritchie, et al., 2020). In Bangladesh after the use of Covishield (similar to Oxford/AstraZeneca), other vaccines that were made available in the country are Pfizer/BioNTech, Moderna and Sinopharm/Beijing. So far, over nine million males and six million females received their first doses of vaccination in the country making up around 11% per 100 people who have received vaccination (DGHS, 2021). In case of second doses, over 3 million men and almost 2 million women have been vaccinated in Bangladesh so far. Covishield and Sinopharm are the most commonly administered vaccines to date.

Chapter 3- Materials and Methods

3.1 Description of the study area

Bangladesh, officially known as the People's Republic of Bangladesh, is a country in South Asia. With an area of 147,570 square kilometers and a population of over 168 million people, it is considered as one of the most densely populated countries in the world. Bangladesh shares borders with India to the east, west and north; Myanmar to the southeast, and the Bay of Bengal to the south. It is separated from Nepal and Bhutan by the Siliguri Corridor and from China by Sikkim, in the north, respectively. Dhaka is the capital and largest city in the country and is considered the nation's economic, political, and cultural hub. Chattogram, on the other hand, is the largest sea port and second-largest city in the country.

3.2 Study Design

A cross sectional study was conducted across the country to investigate the various adverse effects following vaccination for protection against COVID-19. A pre-tested questionnaire was sent out online to different groups and platforms on social media including Facebook, and people across the country were invited to fill out the questionnaire and submit it. Only questionnaires from people matching the case definition were included in the study.

3.3 Case definition

Any person who has never taken any COVID-19 vaccines abroad and has received at least one dose of COVID- 19 vaccine mentioned below in Bangladesh. Fever was further categorized as mild (100.5 to 102.2^0F), moderate (102.2 to 104^0F) and severe (104.1 to 106^0F) (Ogoina, 2011).

3.4 Vaccine composition

The vaccine used was ChAdOx1 nCoV-19 Virus Vaccine (Recombinant). One dose of 0.5ml contains 5×10^{10} virus particles. Other excipients of this vaccine are L-histidine, L-

histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, Ethylene Diamine Tetraacetic Acid (EDTA) and water for injection.

Figure 6: Covishield vaccine

3.5 Vaccine program for the cohort of people

The vaccine is recommended for use in people of 18 years and above. However, in Bangladesh, the first priority of Covishield vaccines were given to healthcare workers and other front liners in this pandemic. All recipients had to register at an online portal with their national identity cards to have access to the vaccine. Thus, the cohort includes healthcare workers; front liners and freedom fighters who are above 50 years of age.

3.6 Criteria for getting into vaccination program

Based on the priority list published by the government of Bangladesh, everyone is eligible for getting in to the vaccination program (BRAC, 2021).

1. Government health workers
2. Non-government health workers
3. Freedom fighters
4. Member of the law enforcement forces
5. Members of the force involved in preventative measures.

6. Essential staff for state management.
7. Elected public representatives
8. Media personnel
9. Employees of the city corporations and municipalities
10. Religious representatives
11. Employees involved in burial services
12. People involved in essential care
13. Employees in sea-rail-airports
14. Government employees from the ministry level to upazillas
15. Bank employees

3.7 Study period

Data was collected from February to April 2021.

3.8 Questionnaire used

A pre-tested semi structured questionnaire was used for this study. The interviewee's demographic features, social history, allergic history, history of co-morbidities was included in the first part of the questionnaire. In the second part, history of contracting COVID-19 before vaccination, vaccination history and adverse effects of vaccination were recorded.

3.9 Data collection

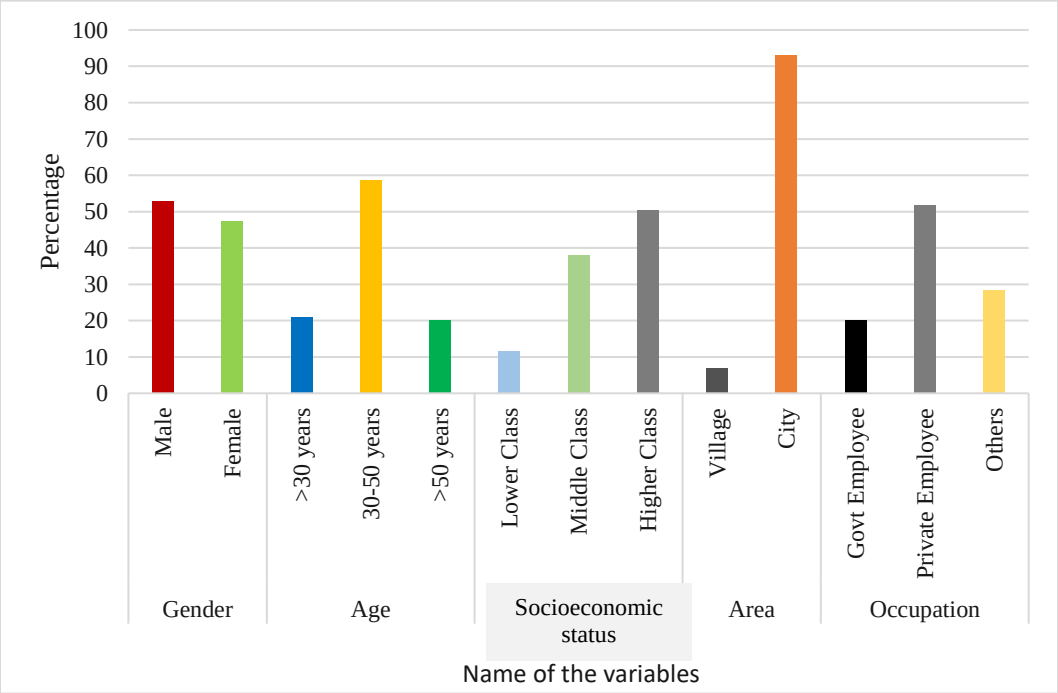
Data was collected both offline and online. For offline forms, study subjects were randomly selected and approached by the principal investigator with the questionnaire. the subjects were interviewed and the questionnaire was filled out by the investigator. For online data collection, the questionnaire was sent out as google forms to various platforms on Facebook. People who were added to these different platforms and choose to respond to this survey accessed the questionnaire, completed them and then sent back. Any questionnaire with missing or incomplete data were excluded from the study. The first 400 consecutive questionnaires that were completed and sent were included as the sample in this study.

3.10 Statistical analysis

All datasets were entered into Microsoft Excel 16 (Excel 2016, Microsoft Corporation, USA). After cleaning and checking the integrity those were imported into STATA/IC-13 software (StataCorp 4905, Lakeway Drive, Texas 77845, USA) for analysis. Univariate association between COVID-19 cases before vaccination and different factors were done by using chi-square test and p value <0.05 were considered as significant. the frequency distribution of different symptoms associated with COVID-19 vaccination were presented as percentage and 95%CI. A bar graph was made to show the pattern of demographical status of vaccine recipients. Bar graphs were also made to display the number of sick days following vaccination; and the interval in days between vaccination and diagnosis of COVID-19.

Chapter 4- Results

Figure 7: Demographic status of COVID-19 vaccine recipient



As illustrated above in **Figure 7** the ratio of male to female respondents were almost the same with a very slight predominance of male respondents. About 58% of the respondents belonged to the 30-50 years age group. Most of the respondents were healthcare workers with a medical background.

For socioeconomic status (SES), more than half of the respondents (50.5%) belonged to the higher class, followed by 38% in the middle class and 11.5% in the lower class.

For employment status, more than half of the respondents (51.75%) were employees at private firms; while 20% were government employees and the remaining were either work independently or are unemployed. Over 90% of the respondents belonged to the city area.

Table 1: Univariate association with the factor and enrolled population who become positive for COVID-19 before vaccination

Variables	Categories	N	n (%)	95% CI	P value
Gender	Male	211	23 (10.9)	7.0-15.9	***0.013***
	Female	189	8 (4.2)	1.8-8.2	
Age	>30 years	84	1 (1.2)	0.03-6.5	***0.000***
	31-50 years	235	16 (6.8)	3.9-10.8	
	>50 years	81	14 (17.3)	9.8-27.3	
SES	Lower Class	46	5 (10.9)	3.6-23.6	***0.001***
	Middle Class	152	2 (1.3)	0.2-4.6	
	Higher Class	202	24 (11.9)	7.7-17.1	
Area	Village	28	2 (7.1)	0.8-23.5	0.901
	City	372	29 (7.8)	5.3-11.0	
Occupation	Govt Employee	80	8 (10)	4.4-18.7	***0.000***
	Private Employee	207	6 (2.9)	1.0-6.2	
	Others	113	17 (15.0)	9.0-22.9	
Smoker	Non- Smoker	235	16 (6.8)	3.9-10.8	0.401
	Smoker	165	15 (9.1)	5.2-14.5	
Allergy	Non-Allergic	364	29 (7.9)	5.4-11.2	0.606
	Allergic	36	2 (5.6)	0.6-18.7	
Diabetes	Non-Diabetic	358	22 (6.2)	3.8-9.2	***0.000***
	Diabetic	42	9 (21.4)	10.3-36.8	
HTN	Non-Hypertensive	345	20 (5.8)	3.6-8.8	***0.000***
	Hypertensive	55	11 (20)	10.4-32.9	
Other comorbidities	No Other Comorbidities	366	28 (7.6)	5.1-10.8	0.807
	Others Comorbidities	34	3 (8.8)	1.9-23.7	

A univariate analysis was conducted between the different factors among the respondents enrolled for the study and their association with becoming positive for COVID-19 before vaccination. Overall, there were more male respondents as compared to female ones. Among them a significant number of male respondents (10.9%) had become positive for

COVID-19 before vaccination as compared to females (4.2%) (p= 0.013). In addition, the number of respondents who became positive for COVID-19 before vaccination increased significantly with aging of the respondent (6.8% in 30–50-year age group and 17.3% in > 50 years age group) (p < 0.001) with only one respondent in the below 30 age group (1.2%). COVID positive cases prior to vaccination in middle class respondents were significantly lower in number (1.3%), and so were the cases of private employees (2.9%) (p= 0.0001). No significant differences were observed based on smoking and allergic history, but respondents with comorbidities such as diabetes (21.4%) and hypertension (20%) had a significantly increased rate in history of being COVID positive before vaccination (p < 0.001).

Table 2: Frequency distribution of sign and symptoms following COVID-19 vaccination

Sign and symptoms	Category	Frequency	Percentage	95% CI
Fever	No Fever	305	76.25	71.8-80.3
	Mild	85	21.25	17.3-25.6
	Moderate	9	2.25	1.0-4.2
	Severe	1	0.25	0-1.4
Vertigo	No	344	86	82.2-89.2
	Yes	56	14	10.7-17.8
Sleepy	No	333	83.25	79.2-86.8
	Yes	67	16.75	13.2-20.8
Lethargy	No	269	67.25	62.4-71.8
	Yes	131	32.75	28.2-37.6
Headache	No	277	69.25	64.4-73.7
	Yes	123	30.75	26.2-35.5
Myalgia	No	247	61.75	56.8-66.5
	Yes	153	38.25	33.5-43.2
Arthralgia	No	281	70.25	65.5-74.7
	Yes	119	29.75	25.3-34.5
Pain in injection	No	125	31.25	26.7-36.0
site	Yes	275	68.75	63.9-73.3
Redness in injection site	No	343	85.75	81.9-89.0
	Yes	57	14.25	10.9-18.1
Swelling in injection site	No	328	82	77.8-85.6
	Yes	72	18	14.4-22.1

Allergy	No	379	94.75	92.1-96.7
	Yes	21	5.25	3.3-7.9
Nausea	No	358	89.5	86.1-92.3
	Yes	42	10.5	7.7-13.9
Vomiting	No	339	84.75	80.8-88.1
	Yes	61	15.25	11.9-19.2
Skin rash	No	371	92.75	89.7-95.1
	Yes	29	7.25	4.9-10.2
Insomnia	No	387	96.75	94.5-98.2
	Yes	13	3.25	1.7-5.5
Sweating	No	357	89.25	85.8-92.1
	Yes	43	10.75	7.9-14.2
Coughing	No	340	85	81.1-88.3
	Yes	60	15	11.6-18.8
Sore throat	No	358	89.50	86.1-92.3
	Yes	42	10.50	7.7-13.9
Diarrhea	No	399	99.75	98.6-99.9
	Yes	1	0.25	0-1.4
Others	No	382	95.50	92.9-97.3
	Yes	18	4.50	2.7-7.0
No of sick days following vaccination	0	51	12.75	9.6-16.4
	1	148	37	32.2-41.9
	2	103	25.75	21.5-30.3
	3	58	14.50	11.2-18.3
	4-6	29	7.25	4.9-10.2
	7-10	11	2.75	1.3-4.8
Severity	No	187	46.75	41.8-51.8
	Yes	213	53.25	48.2-58.2
Hospital admission	No	398	99.50	98.2-99.9
	Yes	2	0.50	0.06-1.8
Medication for complication	No	215	53.75	48.7-58.7
	Yes	185	46.25	41.2-51.2
COVID positive after vaccination	No	377	94.25	91.2-96.1
	Yes	23	5.75	3.9-8.8

The most common symptom following vaccination was pain at the injection site (n=275) followed by myalgia (n= 153), lethargy (n= 131), arthralgia (n=119), and fever (n=95). About half the population (n= 201) developed any form of sickness following vaccination with about half of them (n=103) remaining sick for two days. More than half the

respondents considered the illness to be severe (n=213), however, only two patients required hospital admission for severity of adverse effects. Almost half the patients (n=185) took medications to tackle the adverse effects of COVID-19 vaccine and 23 patients developed COVID-19 infection despite receiving immunization against the disease.

Figure 8: Number of days of sickness following vaccination

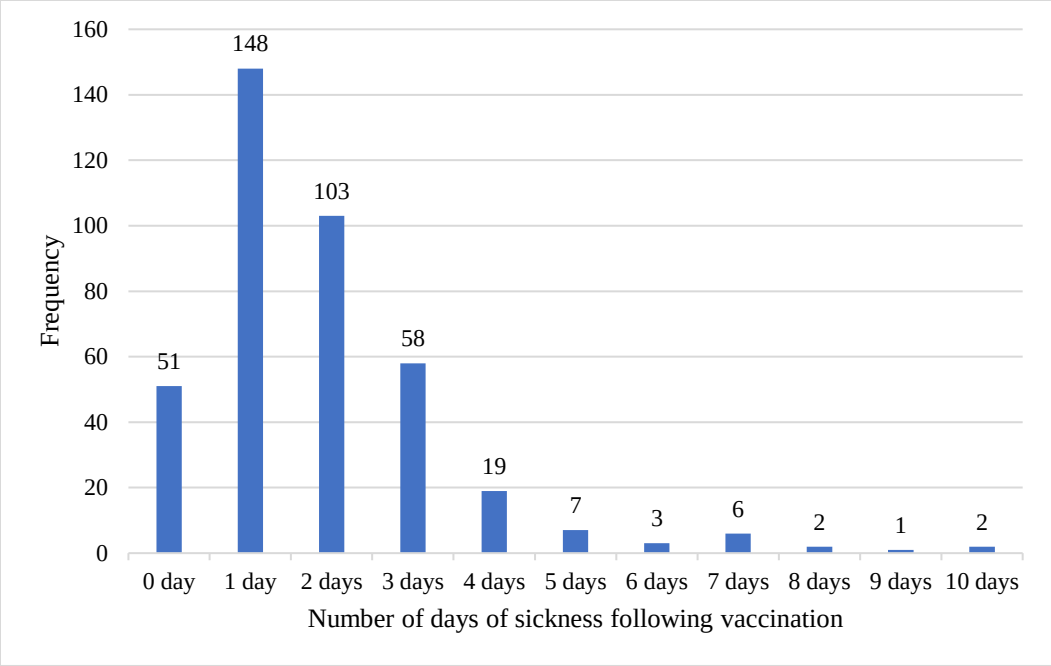
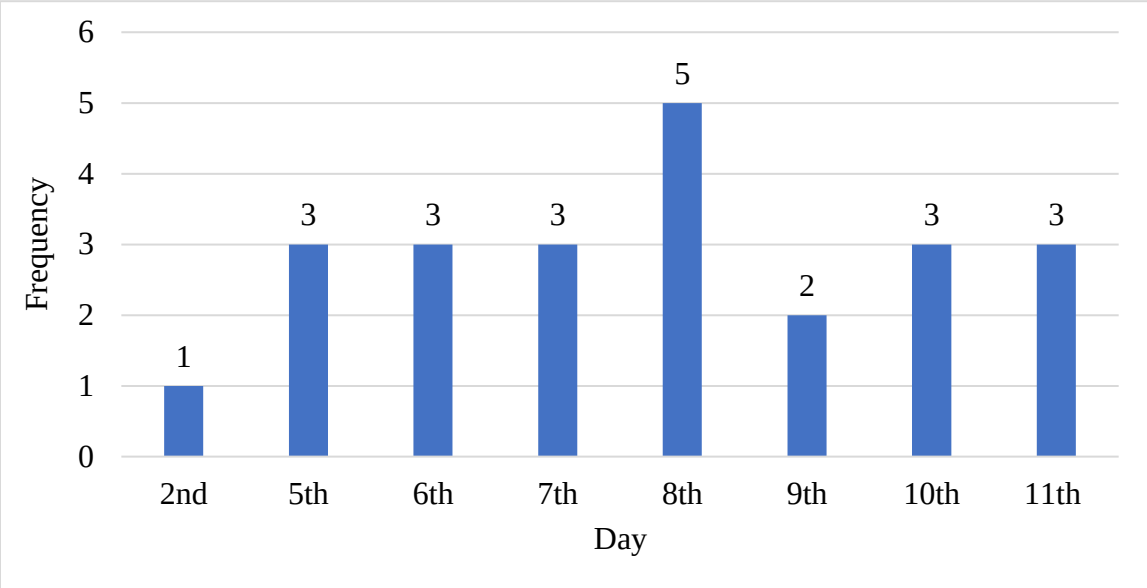


Figure 8 illustrates the number of sick days respondents reported following vaccination. All 400 people who responded to the study had some form of sickness that they reported. The maximum number of days that sickness lasted was 10 days. Among the respondents, the highest frequency of individuals had sickness that lasted for a day(n=148). In 51 respondents, sickness lasted for less than a day following vaccination. The frequency of sick respondents decreased with increase in the number of days following vaccination. More than half the cases had recovered from illness within two days (n= 302). Over 96% of the respondents with illness recovered within five days. Only 5 respondents had illness that persisted for more than a week.

Figure 9: Day of COVID-19 positive after vaccination



In the bar chart above, we observe the number of days that have passed between respondent's vaccination and their diagnosis of COVID-19. Overall, 23 respondents were diagnosed with COVID-19 between 2nd day to 11th day following vaccination. Although the number of cases diagnosed had no significant association with number of days following vaccination, a peak of incidences was observed on the 8th day following vaccination.

Chapter 5- Discussion

COVID-19, a disease caused by SARS-CoV-2 virus, first emerged in Wuhan China (Guo, et al., 2020; Sun, et al., 2020). Since then, it has spread to over 220 different countries disrupting livelihoods and claiming many lives (Worldometer, 2021). This pandemic is a powerful reminder about the ability of a tiny micro-organism to sicken, kill and disrupt, even in well advanced societies that have the best technology. As of 4th October 2021, over 2.9 million new cases were recorded within a week worldwide with highest number of cases as well as deaths in the United States. U.K had the 2nd highest number of cases while Russia had the second highest number of deaths (Worldometer, 2021). In Bangladesh, there were 1,557,964 cases diagnosed between 8th March 2020 and 4th October 2021, and 27,573 COVID related deaths. Currently, Bangladesh ranks 57th in the number of cases and 44th in the number of deaths. Worldwide, the total number of COVID-19 cases have surpassed 235 million among which over 4.8 million cases have already died (Rahman, 2021). The figures are much more critical for the top five infected countries (U.S.A, India, Brazil, U.K and Russia). The increased number of cases along with limited hospital resources to manage them have led to panic and chaos among the general population, further aggravating the situation.

Along with the dramatic losses of lives, this pandemic has led to unique challenges to public health (Kalkowska, et al., 202; Blach, et al., 2021), food systems (Siche, 2020), education and livelihoods globally (Kuhfeld, et al., 2020; Zeshan, 2021). The economic and social disruption caused by this pandemic is unparalleled and quite devastating. Millions of people are out of work and close to extreme poverty. Many of them have become undernourished and developed physical and mental illness (Xiong, et al., 2020; Tee, et al., 2020). Added to this is the burden of solid waste management (Ganguly & Chakraborty, 2021) and inability to control the disease in densely populated developing nations, Bangladesh being one of them. Although methods of disease prevention have been constantly repeated and the general population have been reminded from time to time, lack of compliance has taken the spread of COVID-19 this far.

The only positive aspects of this pandemic observed were the reductions in CO_2 emissions and the return of fossil fuels to its pre-crisis era worldwide (Shan, et al., 2021; Smith, et al., 2021). In China, imposed lockdowns improved the quality of air with satellite data showing a sharp decline in NO_2 levels (Wang & Su, 2020). A similar scenario was observed in India that hold the second largest population in the world. Owing to strict lockdowns, a considerable reduction in levels of NO_2 were

observed. In major cities like Delhi and Mumbai, the emissions have been cut down to almost half the amount observed the previous year. Along with this, a considerable reduction in the consumption of electricity has also been observed in multiple cities (Ghosh, et al., 2020). One study even showed the surface temperature to be reduced by $3\text{-}5^0$ and noise to be reduced from more than 85 decibels to less than 65 decibels (Mandal & Pal, 2020).

To contain the spread of SARS-CoV-2, multiple steps have been implemented by governments of all the affected countries. In order to prevent the spread of infections, protocols have been established both in hospital settings (CDC, 2020) and in the community (Guner, et al., 2020). On a personal level, simple measures such as frequent hand washing and refraining from touching the face could help prevent spread of further infection. In public places, wearing a facemask and maintaining social distancing (at least 3 feet apart) are the best ways to avert disease spread. For healthcare workers at risk of being infected with COVID- 19, CDC and the WHO recommended infection and prevention control measures are implemented. According to this protocol, healthcare workers are advised to wear personal protective equipment at all times and if suspected, they should be rapidly identified and isolated. At the same time all hospital staff and patients have to comply with hand cleaning as well as constant sterilization and disinfection of commonly used items (Yang, et al., 2020). Prevention and control measures have been directed for dealing with all ages and all types of people starting from neonatal exposure (Freitas, et al., 2020) to dealing with COVID-19 infected dead bodies (WHO, 2020). However, non-compliance to COVID-19 regulations have become a major problem in many nations. Studies have shown that individuals with high education and socioeconomic status are more likely to be non-compliant to hygiene related measures (Nivette, et al., 2021).Over confidence is a major reason cited for this increase. According to Hill & Eraso (2021), overconfident people assume they are healthy and not susceptible to infection and intentionally refuse to take preventive measures against the disease. Another reason reported was the necessity to continue work despite showing symptoms of the disease so that income is not lost (Bodas & Peleg, 2020).

With the development of vaccination against COVID- 19, the general population obtained a valuable method of prevention against the disease. Unfortunately, this measure further aggravated the non-compliant situation among the general population with many people assuming they would not catch the disease since they got vaccinated. This raised the incidences of post vaccinated COVID-19 cases and increased the number of secondary carriers. As of July 8th 2021, 3.2 billion COVID-19 vaccinations have been administered globally (Elflein, 2021). However, the pandemic continues to impact countries of the world with further waves of infection and a rising number of

cases worldwide (Elflein, 2021). For controlling the spread of COVID-19, currently 12 vaccines are approved for use (Sah, et al., 2021).But owing to lack of time and the urgent need for a vaccine that works, the duration of trials for these developed vaccines were limited where most trial candidates belonged to one specific race.

Bangladesh received the first consignment of five million COVISHIELD vaccines from India in late January 2021 under an agreement. Prior to this two million doses were gifted to Bangladesh by the same country (Chatterjee , et al., 2021). Thus, the first vaccinations that were given against COVID-19 was Indian manufactured Covishield. This vaccine is similar in structure to AstraZeneca. Trials conducted with this vaccine had few trial subjects from the Asian race. Hence, development of adverse effects and post vaccine complications can also be different based on the body structure and immunity status in our country. Due to lack of information and uncertainty about the adverse events following immunization in our population, people are likely to get discouraged from taking vaccination. This study is an attempt to identify the adverse effects of COVISHIELD vaccination among the population of Bangladesh so that vaccination can be further encouraged among the general population.

In this study a total of 400 people were included as study subjects. Among the respondents, most of them belonged to the 30-50 years age group with a slight male predominance. This is consistent with another study where people aged 25 and above were more likely to accept vaccination globally (Lazarus, et al., 2021). Another plausible reason is that most of the survey results were obtained online and majority of people in the older age groups are unable to use the internet technology efficiently (Charness & Boot, 2009). It could also explain why most respondents belonged to middle or upper classes. Use of internet is comparatively less common in the lower-class population due to low income (Swenson & Ghertner, 2020).On taking a look at the number of respondents who had been diagnosed with COVID-19 before receiving any COVISHIELD vaccine, significant number of male respondents were diagnosed as compared to females.

The proportion of COVID-19 diagnosis reported prior to vaccination were significantly higher among the aged respondents with only one case in the below 30 age group. This was expected from an immunologic perspective due to diminishing T cell responses with age. According to a study by Brodin (2020), the immune systems of young children are adapted to facing new challenges, while older individuals rely more on memory responses. The output of naive T-cells is decreased with the thymus involuting at a rate of around 3% per year. Furthermore, older individuals typically

produce weaker type I IFN responses upon viral infection, allowing the virus to replicate and exhibit a full-fledged infection with increased risk of developing a severe disease condition.

Middle class respondents had significantly lower number of cases, and so had private employees although the causes for these are elusive. All respondents who were diagnosed with COVID-19 before immunization had waited for at least two weeks until their isolation period was over in order to get vaccinated.

The COVISHIELD vaccine consists of 5×10^{10} particles of replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Along with this, the vaccine also consists of excipients such as L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, Ethylene Diamine Tetraacetic Acid (EDTA) and water for injection. These excipients are added either as preservatives (to prevent contamination), adjuvants (to help stimulate a stronger immune response) or stabilizers (to keep vaccine potent during storage and transportation). Yet, these may also cause hypersensitivity reactions and contribute to vaccine side effects. The adverse events following vaccination found in our study was similar to many other studies although the frequency of different adverse effects differed between studies. A total of 19 different side effects were observed in this study. The most common was pain at the site of injection, followed by fever, myalgia, lethargy, headache, arthralgia, swelling at the site of injection and so on. Pain and tenderness in the site of infection is actually the first adverse effect that most individuals experience after being vaccinated. In this study, over 68% of the total study population developed this symptom. This is similar to another study conducted at a specific healthcare center in Dhaka, Bangladesh, where pain at injection site was the most common symptom, although only 32.5% of the respondents had reported such adverse effects (Khalil, et al., 2021). Other common symptoms observed in that study were fever, weakness, malaise, generalized body ache, headache, chills and rigor, and swelling at injection site. In contrast, a study conducted in New Delhi, India showed fever to be the most common symptom followed by pain at the site of injection (Joshi & Singh, 2021). Another study conducted in South India, showed body aches to be the most frequent symptom, followed by headache and fever. Heath care workers of a younger age (19-30 years) and females were more likely to develop adverse events following vaccination (Inbaraj, et al., 2021).

In a study from Nepal, adverse effects of vaccination started at least 4 hours after vaccination. The common symptoms were mood irritability that started after four hours. This was followed by nausea, myalgia, pain and tenderness at injection site and feeling feverish that started around 6

hours post vaccination. It took 12 hours for the development of fevers and chills which had to be relieved by paracetamol. Although fever subsided by the next day, myalgia and pain at site of injection persisted for a few days. No severe adverse effects or deaths were reported due to vaccination (Sah, et al., 2021). In Bangladesh, priority for vaccination was given to high-risk population with healthcare workers being at the top of the list followed by the elderly population and others (BRAC, 2021). Hence, in this study similar outcomes were witnessed and pain at site of injection as well as myalgia were the most common symptoms reported. Likewise, other COVID-19 vaccines such as Pfizer/BioNtech vaccines (Riad, et al., 2021), Moderna, etc. also showed such adverse events. Medications like paracetamol were more likely to be taken with the use of Covishield as compared to other vaccines like Pfizer or Moderna probably due to higher intensity of fever and body aches with this vaccine (Sah, et al., 2021, Joshi & Singh, 2021).

Following injection of vaccine, resident cells, particularly macrophages and mast cells initiate a response within minutes releasing pro-inflammatory cytokines, chemokines, effectors of the complement cascade (C3a and C5a) and vasodilators, including vasoactive amines and bradykinin (Ishii, et al., 2008). Along with cell recruitment from the blood, these vasodilators and chemokines lead to the development of redness and swelling at the site of injection. The neutrophils, monocytes and lymphocytes from the blood adhere to the vessel walls and accumulate at the site of injury through extravasation. These immune cells may then contribute to peripheral nociceptive sensitization by releasing soluble factors, such as cytokines, prostaglandins or ATP, and interact directly with nociceptors to cause pain once threshold is reached. Apart from this, adjuvants that are added with vaccines to enhance immuno-stimulation can also contribute to vaccine reactogenicity by inducing transient systemic innate responses. The mediators at the local site of injection can then spill in to the systemic circulation. In the brain, the induction of cyclooxygenase 2 enzymes and prostaglandin E synthase-1 with these mediators can elevate intracerebral levels of prostaglandin E2. This prostaglandin E2 raises the body temperature and causes after, along with headache, myalgia and chills, all making up the ‘sickness syndrome’ (Hervé, et al., 2019). Other complications such as autoimmune hepatitis (AIH) following vaccination (Rela, et al., 2021) and development of clots (Grant, 2021) are rare instances of vaccination induced adverse effects that have been reported. Very rare cases of AIH were reported In India following vaccination with Covishield, however, recently, cases of AIH have been reported with the use of mRNA vaccines as well. Among the two cases mentioned in the study by Rele. et al. (2021), one survived while the other died. Both developed symptoms between 16 to 20 days post-vaccination. In this study, none of the respondents reported such major complications. One likely reason is that these adverse

effects are extremely rare and the small number of respondents in our study may not have experienced such adverse effects. Generally, adverse reactions to vaccines that are the result of either an immune reaction to a vaccine excipient, the active components of the vaccine or are related to host immunodeficiency are very rare and occur in <1 per million vaccines administered. Simultaneously, increasing attention by the public is focused on these infrequent risks of vaccination (Siddiqui, et al., 2013). For blood clots, one study in the UK reported development of this adverse effect for one in every 250,000 vaccinated people (Mahase, 2021). Incidences of moderate to severe thrombotic complications and thrombocytopenia that resemble heparin induced thrombocytopenia have been reported among patients. This began around one to two weeks following vaccination using Oxford/AstraZeneca. Although the trigger is yet unknown, the serum of such individuals showed variable degrees of platelet activation in the presence of a buffer which was greatly enhanced in the presence of platelet factor 4 (PF4) (Greinacher, et al., 2021).

In spite of these reports, the benefits of taking vaccination outweighs the risks of not taking them. In this study, no individual was found with such complications and no lives were reported lost following vaccine related complications. In fact, most people with adverse effects of vaccination took less than a week to recover with five individuals taking more than a week but up to ten days. While most adverse effects do not last for more than 2 to 3 days, an unusual prolongation of duration of adverse effects can occur in some individuals. One study has reported an association between side effects of COVID-19 vaccine and comorbidities. However, depending on the co-morbidities, the association is either positive or negative. For example, being an asthmatic increased the risk of developing side-effects after the first dose of COVISHIELD vaccine, while having diabetes was not at all a risk factor for development of side effects. This could be due to the decrease in reactogenicity among patients with diabetes mellitus (Remlabeevi, et al., 2021).

A vast majority of adverse events reported following any COVID 19 vaccination can be attributed to development of a protective immune response that is induced by the vaccine rather than an allergic reaction. After entering the body, vaccine antigens are recognized as potential pathogens by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and pattern-recognition receptors (PRRs) such as Toll-like receptors (TLR) (Beutler, 2009) that are found on circulating immune cells (e.g. macrophages and monocytes) and on resident stromal cells (Beutler, 2009) (Moser & Leo, 2010). This causes the cells to synthesize and release pyrogenic cytokines like prostaglandin- E2, interleukins 1 and 6 as well as tumor necrotic factor α in the blood stream just like in cases of infections. Once stimulated, a complex series of immune events such as phagocytosis, release of inflammatory mediators, complement activation, and

cellular recruitment occur. As a result, a strong antigen-specific acquired immune responses is triggered. These events could lead to the development of signs and symptoms such as inflammation at the site of injection of vaccinated people. The products of inflammation can also affect other body systems through circulation thus causing systemic side effects such as fever, headache, lethargy, etc. (Hervé, et al., 2019)In this study it is observed that the adverse events following vaccination for COVID-19 are usually mild with rarely any severe conditions suggesting an immunogenic response.

In COVID-19 infections, although the innate immune system provides essential mechanisms for rapid viral sensing and elimination, the engagement of the adaptive immune response is necessary for efficiently clearing viruses and establishing immunological memory. Two types of immunity are provided by the adaptive immune system: These are humoral immunity (production of antibodies by B cells) and cellular immunity (responses carried out by $CD4^+$ and $CD8^+$ T lymphocytes). Both require antigen presentation in combination with major histocompatibility complex (MHC) and a co-stimulatory signal for full activation (Borges, et al., 2021). Dendritic cells are the most effective antigen-presenting cells that are able to support an innate immune response as well as promote adaptive responses. In covid-19 infections, type I IFN-mediated innate immune responses are necessary for host survival during early phase of infection and dendritic cells are the major source for this. Hence, it is plausible to focus on utilizing these cells for immunogenicity. The two frequently used types of COVID-19 vaccines use dendritic cells to achieve success in vaccination. The first type of vaccine (Pfizer and Moderna) used mRNA technology and lipid nanoparticle (LNP) delivery systems, while the second type (AstraZeneca, Johnson and Johnson, Covishield, Sputnik V) introduced a vaccine consisting of DNA delivered within non-replicating recombinant adenovirus (AdV) vector systems. Both these types of vaccines encode production of the SARS-CoV-2 spike (S) protein, which is the primary target for neutralizing antibodies generated from natural infection. Although phase III clinical trials have showed better efficacy for mRNA vaccines as compared to AdV vaccines, both generated significant neutralizing antibody titers and virus-specific T cell responses within 2–4 weeks after inoculation (Widge, et al., 2021). To stimulate adaptive immunity, a vaccine requires a pathogen-specific immunogen as well as an adjuvant that stimulates the innate immune system and provides the necessary signal for T cell activation. In case of mRNA vaccines, the mRNA serves as both the immunogen and the adjuvant due to intrinsic immunostimulatory properties of RNA. The in vitro transcribed, single stranded mRNA has modified nucleotides to reduce binding to Toll like receptors and immune sensors hence limiting excessive production of type I interferon and its

inhibitory function on cellular translation. The lipid nanoparticles target delivery to lymphatics and promote protein translation in lymph nodes. Once in the lymph node, the lipid nanoparticle that carries the mRNA is engulfed by the dendritic cells which present the antigen to T-cells for activation of the adaptive immune response. AdV vaccines, on the other hand, resides with the viral particle that encases the DNA encoding the immunogen. Following injection, these particles target dendritic cells and macrophages to stimulate an innate immune response. They engage multiple pattern-recognition receptors including those that bind dsDNA, particularly TLR-9 to induce type I interferon secretion (Teijaro & Farber, 2021).

Despite vaccination, there were reports of vaccinated people acquiring Covid-19 with milder symptoms. According to an article by Jain et al (2021), number of factors have been associated with symptomatic or asymptomatic COVID-19 infection after getting vaccinated. These include a high viral load, associated comorbidities, emergence of mutant strains, variants of concern (VOC) that lead to vaccine escape and a casual attitude towards COVID. Among these, appropriate behaviors seemed to be the most important factors for acquiring infection and deaths after COVID-19 vaccination. In case of Covishield, causes of illness following immunization were due to vaccine escape, inefficacy against some mutant strains and vaccine induced immune thrombotic thrombocytopenia (VITT) (Jain, et al., 2021). Hence, it remains important for the public to stay vigilant, continue to follow safety precautions, and adhere to rules and regulations.

After the introduction of COVISHIELD, three more vaccines are currently being administered to the people of Bangladesh. These are Sinopharm, Moderna and Pfizer/BioNTech. However, with the development of newer strains of the virus, a threat of vaccine resistance lurks in our minds. With the added uncertainty of vaccine reactogenicity, convincing the general population to accept vaccination against COVID-19 can become a challenge. Since healthcare professionals are at the frontline of vaccine provisions, they are in an ideal position to promote the benefits of vaccination, predominantly in settings where the fear of adverse effects plays a role in influencing decisions to vaccinate. Reporting adverse effects following immunization, even if they are already in the prescribing information, is an important mechanism by which healthcare professionals contribute to the continuous monitoring of vaccine safety. While we know that a certain level of inflammation is needed to trigger an effective adaptive immune response, we do not yet know how to quantify that level, or predict how this translates into reactogenicity (Hervé, et al., 2019). Identification of biomarkers that are linked to reactogenicity can help us further understand the connection between reactogenicity and immunogenicity. In the future, this could help us introduce new vaccines which exhibit lower adverse effects. It could also help us identify beforehand which individuals are more

likely to experience more severe symptoms after vaccination so that precautions can be taken earlier.

Chapter 6- Conclusion

Our study demonstrated that the frequently observed adverse effects following vaccination were pain at injection site, myalgia, arthralgia, fever and lethargy. Significant risk factors associated with the development of COVID- 19 infections were male gender, older age, comorbidities like hypertension and diabetes, socioeconomic status (higher class or lower class) and occupation (government employee). Despite vaccination, 23 cases developed COVID-19 where the diagnosis was made within 11 days of vaccination with a peak on the 8^{th} day.

Chapter 7- Limitations

Since the study was conducted based on online survey, however, respondents who knew how to access the survey and answer questions in the questionnaire could respond. Therefore, literacy of the respondents and opinions of respondents who were born and brought up in adverse environments could not be evaluated in this study. All the data was based on the respondent's opinion and no COVID-19 test result could be checked to confirm the respondent's claims. Hence, this study is liable to respondent bias. By the time this study was conducted and data was being collected, most of the population received only one dose of the vaccine, hence the adverse effects reported were based on only the first dose of vaccination. As a result, a comparison between first and second doses of vaccines within the same respondent and among respondents could not be evaluated. The follow up period after the first dose of vaccine was less than a month for most cases, hence, it is difficult to confirm how many more respondents developed COVID-19 following vaccination after the questionnaire was completed. Since at the time of our study, Covishield was the only vaccine given, a comparison between adverse effects among people receiving different vaccines could not be assessed.

Chapter 8- Recommendations

Further research on the efficacy of this vaccine is necessary. Since newer strains of the COVID-19 virus is constantly emerging, it is very crucial for an efficient vaccine to be developed. Unfortunately, as most vaccines were developed with limited trials and distributed in the market, long term adverse effects and the clinical profile of partially or completely vaccinated COVID-19 patients need to be evaluated in prospective studies. Comparative studies between outcomes of people vaccinated with different COVID-19 vaccines within our population would be a tremendous approach in identifying which vaccine works best for our population. Nevertheless, research on to prevention of COVID-19 is still an ongoing process and with the pandemic still at large, these investigations will not end so soon.

Chapter 9- Reference

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