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CHAPTER TWO

Coronavirus reinfections: An outlook on evidences and effects

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1 Introduction

A sudden increase in the number of patients, diagnosed with pneumonia and respiratory distress, more-so-over with unknown etiology were reported in December 2019, from Wuhan city, Hubei province, China. In February 2020, World Health Organization (WHO) announced it as a "Public Health Emergency of International Concern" and termed it COVID-19 (World Health Organization, 2020; Wu and McGoogan, 2020). Coronaviruses (CoVs) belong to the *Coronaviridae* family, the enveloped viruses that own unusually long single-stranded RNA genomes varying from 26 to 32 kilobases in length (Zheng, 2020; Su et al., 2016). The Coronavirus family has shown a high transmission and infection rate in humans; at present seven Coronavirus species have been identified to produce illness in humans. The four members of CoVs family (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) are responsible for producing a variety of upper respiratory tract infections with common cold symptoms which are mild, and the remaining three viruses, i.e., Severe Acute Respiratory Syndrome-Coronavirus-1 (nSARS-CoV-1), Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome-Coronavirus-2 (nSARS-CoV-2) leads to an atypical pneumonia (Su et al., 2016). SARS-CoV was recognized in 2003, began in China spread to more than 30 countries with more than 8000 cases and 774 deaths worldwide (Drosten et al., 2003; Zhong et al., 2003). MERS-CoV was recognized in 2012 in Saudi Arabia and Jordan, spread more than 27 countries with nearly 2500 cases and 850 related deaths (Zaki et al., 2012). SARS-CoV-2 is a novel Coronavirus that has been identified as the causative organism of Coronavirus disease 2019 (COVID-19), which started in late 2019 in Wuhan, China and expanded globally (Su et al., 2016). Currently; as of

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August 05, 2021, the WHO has reported more than 200 million cases and more than 4.26 million deaths globally. The condition of severe pneumonia is visible more likely in the elderly and individuals with clinical irregularities like hypertension, diabetes, CHF, renal failure, etc. All the COVID-19 treatment options of prescribing drugs are based on the experiences gained from SARS, MERS or other new influenza viruses. Hence, there is a crucial need to diminish the spread of the virus by adopting all kinds of preventive and control methods, like social distancing, wearing masks and gloves etc.

2 Coronavirus reinfection

The Coronavirus reinfection means a person was infected once, recovered, and then again became infected due to reactivation of the virus in patient body or attack of genetically different mutant virus. The reinfection was confirmed by epidemiological, clinical, serological, and genomic analyses of continual viral shedding from the first infection (To et al., 2020). The COVID-19 reinfection cases were reported in various regions of the world such as Hong Kong, South Korea, China, Taiwan, Japan, Russia, United States of America, Qatar, Belgium, Ecuador, Brazil, Mexico, Israel, Canada, Switzerland, Sweden, Colombia, Germany, European countries, and India (BNO News, 2021). The world's first COVID-19 reinfection was documented/confirmed in Hong Kong in an adult patient, 33-year old male (To et al., 2020) and the second case was confirmed in Belgium in a 50-year old woman on the same day with the asymptomatic and mild symptoms (Table 1).

The next four cases of Coronavirus reinfections were documented in Netherlands with mild to severe infection. The first case of reinfection in United States was confirmed on August 28, 2020, in a 25-year old man infected with serious symptoms (Tillett et al., 2021). The second case of reinfection in the United States was reported in 45-year old man with notable worse reinfection (Larson et al., 2020). An Indian scientist reported the two genetically confirmed cases of reinfection, one is 25-year old man and second is 28-year old woman, and both were asymptomatic (Gupta et al., 2020). Four additional cases of reinfection were reported with Indian health workers involved in the treatment of COVID-19 patients at Mumbai, who suffered from mild symptoms during the reinfection (Shastri et al., 2020) (Table 1). As per COVID-19 reinfection tracker data published by BNO news, there were 84 cases, 03 deaths, 59 recovered patients, along with more than 40,000 suspected cases and more than 100 deaths till June 02, 2021

Table 1 Reported cases of reinfection (first 30) in world.

S. No.	Reported date[a]	Location	Patient Age/Sex	Interval[b]	Symptoms (1 Case)	Symptoms (2 Case)
1	24 Aug 2020	Hong Kong	33/M	123 days	Mild	None
2	24 Aug 2020	Belgium	51/F	93	Mild	Mild
3	24 Aug 2020	Netherlands	60+	NA	NA	NA
4	26 Aug 2020	Netherlands	60+	60 days	NA	NA
5	26 Aug 2020	Netherlands	80/M	21	Mild	Mild
6	26 Aug 2020	Netherlands	60/M	12 days	Mild	Serious
7	28 Aug 2020	United States	25/M	31 days	Mild	Serious
8	30 Aug 2020	Euador	46/M	47 days	Mild	Moderate
9	15 Sept2020	India	28/F	100 days	None	None
10	15 Sept 2020	India	25/M	101 days	None	None
11	23 Sept 2020	United States	42/M	51 days	Mild	Serious
12	23 Sept 2020	India	24/F	48 days	Mild	Mild
13	23 Sept 2020	India	27/M	13 days	None	Mild
14	23 Sept 2020	India	31/M	59 days	None	Mild
15	23 Sept 2020	India	27/M	60 days	Mild	Mild
16	29 Sept 2020	Qatar	20/M	54 days	NA	NA
17	29 Sept 2020	Qatar	40/F	87 days	NA	NA
18	29 Sept 2020	Qatar	40/M	70 days	NA	NA
19	29 Sept 2020	Qatar	20/M	45 days	NA	NA
20	30 Sept 2020	Belgium	30/M	143 days	Mild	Mild
21	30 Sept 2020	Belgium	25/F	115 days	Mild	Mild
22	12 Oct 2020	Netherland	89/F	54 days	Moderate	Serious
23	14 Oct 2020	Spain	62/M	147 days	Mild	Serious
24	16 Oct 2020	Sweden	53/F	120 days	Mild	Mild
25	10 Nov 2020	Belgium	30/F	185 days	Mild	Mild
26	21 Nov 2020	South Korea	21/F	10 days	Mild	Mild
27	09 Dec 2020	Brazil	37/F	116 days	Mild	Mild
28	11 Dec 2020	Peru	6/F	97 days	Mild	Mild
29	16 Dec 2020	Brazil	41/F	145 days	Mild	Mild
30	17 Dec	Mexico	M	64 days	Mild	Mild

[a]The month in which reinfection is made public. Due to the time needed to establish reinfection, the actual case may have happened weeks or months earlier.
[b]The length of time between the first case's recovery and the second case's start of symptoms, if known. Unless otherwise specified, the number of days between confirmed cases.
https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/.

(BNO News, 2021). The Qatar research team has confirmed four cases of reinfection in the world's largest investigation till date with more than 130,000 positive tests and these findings suggested that SARS-CoV-2 reinfection can occur, but it is an exceptional observation in which the majority of infected persons develop immunity against reinfection that remains for a

period of few months after primary infection (Abu-Raddad et al., 2020). The studies of the Indian Council of Medical Research (ICMR) have found that 4.5%, (58 of the 1300 individuals) could be most probable cases of reinfection of SARS-CoV-2 in India (Mukherjee et al., 2021). People who suffered from COVID-19 have got 84% protection from COVID-19 reinfection and 93% protection from COVID-19 symptomatic infection during 7 months of follow-up as per studies in healthcare workers in England (Hall et al., 2021).

3 Reinfection and genome sequence

The virus that causes COVID-19, SARS-CoV-2, is one of many viruses that mutate throughout time. Most changes have little or no impact on the virus's properties. On the other hand, specific changes may affect the virus's features, such as the ease with which it spreads, the severity of the illness it causes, or the effectiveness of vaccines, therapeutic medicines, diagnostic instruments, and other public health and social interventions (World Health Organization, 2021). The study of COVID-19 whole genome sequencing (WGS) data has provided valuable information regarding the growth, functioning, and mutation of organisms; it can be applied for diagnosis, control, treatment, and development of vaccine. The genome of Coronavirus is the largest among identified RNA viruses (27 to 31.5 kb) with 29,903 nucleotides and it is polycistronic, consisting of sub-genomic RNAs with regular 5 and 3 sequences (Li et al., 2005; Paraskevis et al., 2020). The first complete genome sequence of the SARS-CoV-2 isolated from human cases from China was reported on January 05, 2020 by China (Wu et al., 2020b) and currently, thousands of genomes sequences have been reported till date. The various scientific investigations has reported that both times COVID-19 patients were infected with the viruses had differences in some of their genes caused by antigenic drift, antigenic shift, and recombination known as natural mutations (Baxi and Saxena, 2020). The Hong Kong case provides the first documentary evidence and confirmed that different viral strains are responsible for reinfection (To et al., 2020). The reinfection was reported from Nevada, in the US, where five nucleotides are muted from the first SARS-CoV-2 Coronavirus genomes, i.e., five single point mutations were found as compared to the reference genome sequence from the first infection (Tillett et al., 2021). There is, however, an indication of SARS-CoV-2 reinfection without changes in the virus's spike protein (Kulkarni et al., 2021). The WHO and its worldwide expert networks

are monitoring viral evolution, searching for variations that represent a greater danger to global public health and are designated as Variants of Concern (VOC) or Variants of Interest (VOI) (Table 2). The WHO defines VOC as a rise in transmissibility or detrimental transformation in COVID-19 epidemiology and a surge in virulence or a reduction in diagnostic, vaccine, or treatment efficacy. The WHO defines VOI as viruses that have undergone genetic modifications that are expected or reported to affect virus attributes such as infectivity, disease severity, immune escape, diagnostic or therapeutic escape, and have been identified as causing major community transmission in numerous nations (Table 2). The Alpha, Beta, Gamma, and Delta variants fall under VOC, whereas Eta, Iota, Kappa, and Lambda fall under VOI (World Health Organization, 2021). The B.1.1.7 variant and B.1.1.28 SARS-CoV-2 variant viruses have been circulated in numerous countries and caused reinfection in Brazil, United Kingdom and South Africa (Toovey et al., 2021). The delta variant (B.1.617.2) of Coronavirus which was in circulation during the second wave pandemic in India is significantly less sensitive to immunity from a previous infection or vaccination. According to Public Health England (PHE), the risk of reinfection with delta variant is 46% higher than the Alpha variant, with the highest risk

Table 2 The WHO designated variants of concern (VOC), and variants of interest (VOI).

WHO class	WHO label	Pango lineages	Earliest documented samples	Date of designation
Variant of Concern (VOC)	Alpha	B.1.1.7	United Kingdom, Sep-2020	18-Dec-2020
	Beta	B.1.351, B.1.351.2, B.1.351.3	South Africa, May-2020	18-Dec-2020
	Gamma	P.1, P.1.1, P.1.2	Brazil, Nov-2020	11-Jan-2021
	Delta	B.1.617.2, AY.1, AY.2	India, Oct-2020	VOI: 4-Apr-2021, VOC: 11-May-20
Variants of Interest (VOI)	Eta	B.1.525	Multiple countries, Dec-2020	17-Mar-2021
	Iota	B.1.526	United States of America, Nov-2020	24-Mar-2021
	Kappa	B.1.617.1	India, Oct-2020	4-Apr-2021
	Lambda	C.37	Peru, Dec-2020	14-Jun-2021

seen six months after a first infection. The delta variant second infection was 2.37 times more common than with Alpha.

The possibility of reinfection may be raised in the coming time as the immune system does not have any memory of variant strains of SARS-CoV-2. Therefore, genome sequencing of SARS-CoV-2 is necessary to understand why this virus is behaving differently. As a significant number of people reinfected from COVID-19 infection are asymptomatic, without under surveillance and lack of genomic sequencing studies may make it impossible to estimate the real numbers of reinfections. The reinfection or reactivation of COVID-19 patient with asymptomatic or mild symptom unintentionally spread the virus in the environment and leads to infection of other healthy people. Intensive research on COVID-19 reinfection is urgently needed to elucidate the probability, frequency, severity, and effect on immunity and vaccine development. Hence, this chapter focuses on recent progress on COVID-19 reinfection, its severity, frequency, immunopathogenesis of Coronavirus infection, immune response on reinfection and its effect on the development of vaccine and herd immunity.

4 Immunopathogenesis of Coronavirus infection

The SARS-CoV-2 initiates its response and causes severe damage to the respiratory tract. The spike glycoprotein of the virus binds with the ACE2 receptors on the alveolar epithelium infecting respiratory tract cells, epithelial hair cells of airways and type 2 alveolar pneumocytes, causing immune cells (monocytes, macrophages and neutrophils) infiltration and release of pro-inflammatory cytokines (IL-1, Il-6, IL-12, TNF, TNF-α, INF-γ) and chemokines (CCL2, CXCL, CXL10). These events (generally known as cytokine storm) seem to be responsible for causing diffused alveolar damage through edema, fibrosis, hyaline membrane formation, and ultimately alveolar collapse, desquamation of epithelial and alveolar cells, and multiple organ injury (Fig. 1) (Chen et al., 2020; Wang et al., 2020).

When antigen-presenting cells (dendritic cells or macrophages) identify the SARS-CoV-2 virus, T-lymphocytes become stimulated and produce inflammatory mediators (IFN-I, TNF-, IL-1, IL-6, CCL2), as well as perforin and granzyme B (Kumar et al., 2020). Lymphopenia is mostly identified in the acute phase of infection (Fathi and Rezaei, 2020). However, in severe cases, excessive release of inflammatory mediators (cytokine storm) intensifies the inflammatory response causing lung injuries leading to respiratory collapse, organ failure and eventually death (Song et al., 2020). This is

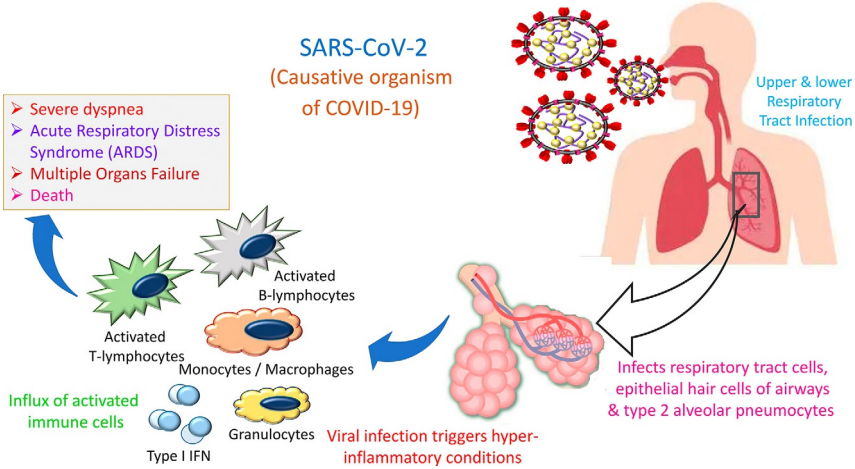

Fig. 1 Human immune response during SARS-CoV-2 infection.

also supported through inflammatory infiltration, carried out by macrophages and neutrophils. The prevalence of immune response directed by immune cells becomes severe in the latter stage of the infection. Basically, immune cells participate in an innate immunity and activate adaptive immune response. The immune response fails to activate T cells during SARS-CoV-2 infection (Oliveira et al., 2020). The constant stimulus initiated by viral infection urges the cells to generate inflammatory mediators to diminish the viral replication, though the event end up exaggerating the pathogenesis with severe tissue damage (Fig. 2) (Shirbhate et al., 2020).

5 Reinfection and immune response

The immune system becomes activated on infection, wherein initially innate immunity fights against infection. If infection still persists, the adaptive immunity plays its role for abolishing the infection. All the infections, primarily activates innate immunity wherein, white blood cells causes inflammation and produces primary antibodies to kill the virus from body. If infection persists for a longer time then adaptive immunity (antigen-specific immune response) involving T cells and B cells identifies the antigens derived from virus. The role of T cells is to sense and kill the infected cells, whereas B cells produce antibodies that kill the virus. In a healthy adult, the coordinated $CD4^+$ T cell, $CD8^+$ T cell and antibody responses are protective against infection, but this coordination frequently fails in the aged

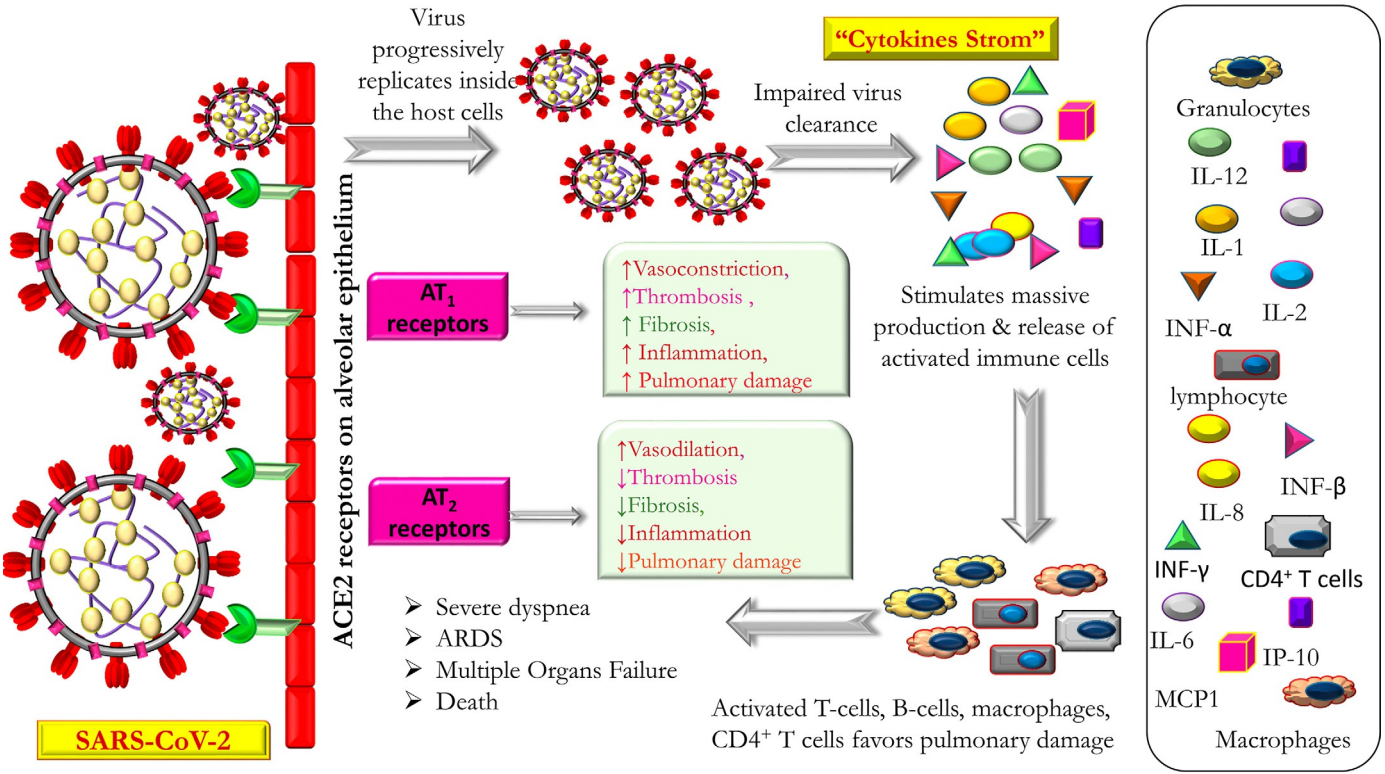

Fig. 2 Mode of action of SARS-CoV-2.

population, leading to impaired adaptive immune response to SARS-CoV-2. The milder symptoms of COVID-19 infection are associated with $CD4^+$ T cells and $CD8^+$ T cells (Fig. 2) (Moderbacher et al., 2020). Some of these T cells and B cells, known as memory cells exist for a longer duration after recovery from infection. Thus, adaptive immunity includes memory that ensures future responses against SARS-CoV-2 reinfection.

Scientific research on the humoral immune response to SARS-CoV-2 indicates that adequate antibody levels are present and they do not decline during the period of three to four months after the diagnosis of COVID-19 in a person thus there is no clinical reinfection within this period (Gudbjartsson et al., 2020; Mumoli et al., 2020; Van Elslande et al., 2020). Additionally, some scientific reports indicate that protective immunity is only for a short period of time and leaves us more exposed to the virus reinfection (Table 1). Edridge et al. studied the duration of acquired immunity suffered from four seasonal Coronaviruses (HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU), and reinfection was observed regularly at 12 months after infection (Edridge et al., 2020).

6 Severity and risk of Coronavirus reinfection

The spreading ability rate of different genetically or mutant Coronavirus will increase with time and could lead to increased COVID-19-reinfected patients. The majority of COVID-19 reinfection cases have been described as asymptomatic or with lesser illness severity than the first infection, confirming the notion that natural immunity may mitigate disease incidence even when it does not completely avert reinfection (Van Elslande et al., 2020; Long et al., 2020). However, some COVID-19 reinfection cases have been disclosed with moderate and severe reinfection (Table 3) symptom along with 03 deaths reported in the Netherlands, Israel, and Brazil (BNO News, 2021). The people suffering from COVID-19 infection may not be protected for a longer period against the virus reinfection due to low immunity, tapered antibody response, and increased susceptibility to virus infections. The interval between the first and second infection varied from 10 days to 334 days in reported cases (Table 3) (BNO News, 2021). Various scientists reported that the antibodies stay for 3–6 months after COVID-19 infection. The COVID-19 asymptomatic or mild symptomatic patients are at the most risk of reinfection because those patients activate only innate immunity, which provides partial protection against COVID-19 reinfection. When patients have significant viral replication in their bodies,

Table 3 COVID-19 infections and treatment guidelines.

S. No.	Class of COVID-19	Symptom	Treatment
1	Asymptomatic or Presymptomatic infection of COVID-19	No symptoms	Complete home isolation, nutrient diet and antioxidant-rich beverages. Immunity-boosting supplements comprising of zinc, multivitamins, vitamin C. Routine check-up of temperature and oxygen saturation (SpO_2) level and informing health authorities, if they have low saturation (less than 94) or high temperature.
2	Mild infection of COVID-19	Fever, cough, sore throat, malaise, headache, muscle pain, vomiting, diarrhea, loss of taste and smell. Not have shortness of breath, dyspnea, or abnormal chest imaging.	Self-isolation at home, manage treatment through telemedicine or telephone visits. Symptomatic treatment such as antipyretics for fever and pain, multivitamins, adequate nutrition and appropriate rehydration.
3	Moderate infection of COVID-19	Lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2). 90% to <93% on room air at sea level. Respiratory rate > 24/min, breathlessness, not require emergency interventions or hospitalization.	Isolation is necessary. High risk patients at deterioration, isolation in hospital is preferred. If bacterial pneumonia or sepsis is suspected, empiric antibiotic treatment should be used followed by regular re-evaluation of the patient. Antibiotics should be avoided, if there is no bacterial infection.
4	Severe infection of COVID-19	Obstructed breathing, severe respiratory distress, central cyanosis, shock, coma and/or	Immediate supply of oxygen to patients with emergency signs. If secondary bacterial

Table 3 COVID-19 infections and treatment guidelines—cont'd

S. No.	Class of COVID-19	Symptom	Treatment
		convulsions. The patients have $SpO_2 < 90\%$, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, respiratory rate > 30 breaths/min, or lung infiltrates >50%.	pneumonia or sepsis is there antibiotics may be used till any infection persists. Fluid management is required in patients with COVID-19 without tissue hypoperfusion and fluid responsiveness.
5	Critical infection of COVID-19	Respiratory failure, septic shock, and/or multiple organ malfunction.	Application of non-invasive or high-flow nasal oxygen (HFNO) systems. Management of medical condition that has resulted in ICU admission and other comorbidities and hospital acquired infections.

adaptive immunity is activated, and they have a difficult recovery but acquire long-term immunity (Li et al., 2020; García, 2020). The immune compromised persons have impaired antibody response, may not develop sufficient antibodies after infection, having higher risk of COVID-19 reinfection. A Diabetes patient who have had a previous COVID-19 infection have a faster fading immunity, putting them at a greater risk of reinfection than those who do not have diabetes (Pal and Banerjee, 2021). Thyroid disease which affects hormonal and immune system function, reduces the body's capacity to fight infections and other pathogens, increasing the chance of reinfection with COVID-19. The treatment of thyroid can suppress the immune system functioning, make a person vulnerable to catching frequent illnesses (Lisco et al., 2021). Obese people infected with COVID-19 raise inflammatory levels in the body, disrupt essential functioning, and make it much more difficult for the immune system to generate sufficient

antibodies, especially after recovering from COVID-19 infection. However, if obese persons receive the vaccination, the outcomes may not able to generate sufficient antibodies. As a result, they are at the greatest risk of reinfection and difficulties following recovery (Mohammad et al., 2021; Popkin et al., 2020). Frontline and healthcare workers are more exposed to COVID-19 virus variants than the general public, putting them at higher risk of reinfection.

7 Management strategies and guidelines for COVID-19 reinfection

Re-infection should be treated similarly to the first COVID-19 infection. Patients infected with SARS-CoV-2 should be classified according to the degree of their illness, with cases being classified as asymptomatic/presymptomatic, mild, moderate, severe, or critical infections and treated appropriately. The standards for each group might overlap or differ in clinical guidelines and trials. Moreover, the clinical condition of a patient might vary with time. COVID-19 reinfected patients always possess severe infection along with compromised lung situation, so they necessitate additional care and examination as compared to primary infected patients.

7.1 Asymptomatic or pre-symptomatic infection of COVID-19

The asymptomatic or pre-symptomatic patients do not possess any primary symptoms, but they are still carriers of the COVID-19 infection and may put other people's lives at risk. These patients need strict home isolation with no contact with any family members, nutrient-rich diet with plenty of fruits and vegetables, and drinking fluids rich in antioxidants. The patients should take immunity-boosting supplements containing zinc, multivitamins, especially vitamin C. The patient should also regularly monitor the temperature and oxygen saturation (SpO_2) and inform to health authorities, if they have low saturation (less than 94%) or higher body temperature.

7.2 Mild infection of COVID-19

The patients with mild infections show a range of symptoms such as fever, sore throat, cough, loss of taste and smell, headache, muscle pain, malaise, nausea, vomiting, diarrhea etc. These patients do not have choking of breath, dyspnea on hard work, or atypical imaging. The majority of mildly infected patients can be treated at home in self-isolation. The telemedicine or telephone visits could be used to treat symptomatic patients using

antipyretics for fever and pain, multivitamins, sufficient nutrition, and appropriate rehydration. The health monitoring team should observe elderly patients and susceptible persons directly until clinical recovery is attained.

7.3 Moderate infection of COVID-19

Patients with moderate infection exhibit lower respiratory illness (such as bronchitis or pneumonia) on clinical examination or imaging, an oxygen saturation (SpO_2) level of 90% to 93% on room air at sea level, a respiratory rate more than 24 breaths per minute, and dyspnea. As lungs disease deteriorates rapidly in patients with COVID-19, so they should be monitored closely. If moderately infected COVID-19 patient have bacterial pneumonia or sepsis, then following steps should be considered: (i) empiric antibiotic treatment should be administered, (ii) the patient should be re-evaluated every day, and (iii) When there is no evidence of bacterial infection, antibiotics should be reduced or discontinued. If the condition of COVID-19 deteriorates, isolation in hospital is preferred.

7.4 Severe infection of COVID-19

Patients infected with COVID-19 are classified as having a severe infection if they meet one or more of the following criteria: (i) SpO_2 level less than 90% on room air at sea level, (ii) a respiratory rate more than 30 breaths/min, (iii) PaO2/FiO2 less than 300 mmHg, or lung infiltrates higher than 50%. These patients may have fast clinical worsening. Medical oxygen should be administered instantly by means of a nasal cannula or a high-flow oxygen apparatus. Standard drug therapy for COVID-19 patients is recommended as per specific therapy guidelines prescribed by local authorities. If severe infected COVID-19 patient have bacterial pneumonia or sepsis then following steps should be considered: (i) empiric antibiotic treatment should be administered, (ii) the patient should be re-evaluated every day, and (iii) When there is no evidence of bacterial infection, antibiotics should be reduced or discontinued.

7.5 Critical infection of COVID-19

Critically ill person may include short term respiratory distress syndrome, virus-induced distributive shock, cardiac malfunction, precipitation of inflammatory condition, and/or worsening of comorbidities. The patients with critical infection may have disorders of the respiratory, cardiac, hepatic, renal, and central nervous system. The critically ill patients admitted to

intensive care unit (ICU) requires proper clinical treatment of both the medical condition that primarily disease and other comorbidities including hospital acquired infections (if any).

8 COVID-19 reinfection and vaccine development

The vaccination of humans mimics the primary infection through antigens that attack on adaptive immune system and produces memory cells that could be stimulated quickly in the case of actual infection. Hundreds of vaccine candidates are being tested in clinical trials to evaluate their safety and efficacy. At present, 17 vaccines are approved across several countries out of them 06 vaccines are approved by WHO (Covid19 Vaccine Tracker, 2021) (Table 4). The Immunologists reported that the immune response to Coronaviruses is complex. Immune cells play an vital role in remembering the previous infection and shielding the patient from demising to reinfection, as the time progress immunity will fade, leaving us more exposed to the Coronavirus reinfection (Yan et al., 2021). The reinfected COVID-19 patients have asymptomatic or milder infection in the second time; this indicates that the immune system is responding, while not defending us against it for the longer duration. At present, a number of cases have been reported who were vaccinated but suffered from COVID-19, indicating that existing vaccines do not provide protection against infection,

Table 4 List of approved vaccine by at least one country.

S. No.	Vaccine name	Company	Type	Approval
1	AZD1222	Oxford-AstraZeneca	Non Replicating Viral Vector vaccines	WHO, 119 Countries
2	BNT162b2	Pfizer-BioNTech	RNA vaccines	WHO, 97 Countries
3	Ad26.COV2·S	Johnson & Johnson	Non Replicating Viral Vector vaccines	WHO, 56 Countries
4	mRNA-1273	Moderna	RNA vaccines	WHO, 64 Countries
5	BBIBP-CorV	Sinopharm (Beijing)	Inactivated virus vaccines	WHO, 59 Countries
6	Covishield	Serum Institute of India	Non Replicating Viral Vector vaccines	WHO, 45 Countries

Table 4 List of approved vaccine by at least one country—cont'd

S. No.	Vaccine name	Company	Type	Approval
7	RBD-Dimer	Anhui Zhifei Longcom	Protein subunit vaccines	2 Countries
8	Covaxin	Bharat Biotech	Inactivated virus vaccines	9 Countries
9	KoviVac	Chumakov Center	Inactivated virus vaccines	1 Country
10	EpiVacCorona	FBRI	Protein Subunit vaccines	2 Countries
11	Ad5-nCoV	CanSino	Non Replicating Viral Vector	8 Countries
12	Sputnik V	Gamaleya	Non Replicating Viral Vector	70 Countries
13	QazVac	Kazakhstan RIBSP	Inactivated virus vaccines	1 Country
14	SARS-CoV-2 Vaccine	Minhai Biotechnology Co	Inactivated virus vaccines	1 Country
15	Inactivated (Vero Cells)	Sinopharm (Wuhan)	Inactivated virus vaccines	1 Country
16	CoronaVac	Sinovac	Inactivated virus vaccines	39 Countries
17	TAK-919	Takeda	RNA vaccines	1 Country
18	CIGB-66	Center for Genetic Engineering and Biotechnology	Protein Subunit vaccines	1 Country
19	MVC-COV1901	Medigen	Protein Subunit vaccines	1 Country
20	COVID-19 Inactivated Vaccine	Shifa Pharmed Industrial Co	Inactivated virus vaccines	1 Country
21	Sputnik Light	Gamaleya	Non Replicating Viral Vector	12 Countries

while it provide protection against the severity of COVID-19 illness. This makes the existing vaccines capable of reducing serious complications of COVID-19, the need for hospitalization and mortality. Recent research suggests that prior COVID-19 infection may not completely protect children and adolescents from reinfection, and immunization is still required

to enhance immune responses, minimize reinfection, and decrease spread (Letizia et al., 2021).

The COVID-19 reinfection arise questions for the developers of COVID-19 vaccines, i.e., efficacy of genetically different stain and mutant viruses, durability of immunity and safety (immune response can facilitate future infections). The Coronavirus mutations occurring in T-cell and B-cell epitopes or in proteins as component of the host-viral interactome, might hinder vaccine or drug effectiveness in limited people (Singh et al., 2020). The researchers need to develop new generations of vaccines able to prevent from antigenic drift and shift, as performed with the flu. During the 2009 pandemic of a rising influenza A virus (IAV; H1N1pdm09), scientists found that in the months, when both the rhinovirus and the influenza virus were active, the influenza virus was absent if the rhinovirus was present (Wu et al., 2020a). These outcomes showed that one respiratory virus can obstruct the infection with another by activating the antiviral defenses in the respiratory epithelium, confirming the fact that intervention from rhinovirus disrupted the 2009 IAV pandemic in Europe. Later findings showed that viral intervention might possibly have an effect on the course of an epidemic, and this approach could be considered during the design of interventions for continuing COVID-19 pandemic. Recent studies of dengue antibodies may lend some level of immunity against the novel Coronavirus (Nicolelis et al., 2020). Another approach is to design vaccine with seasonal shots of vaccine with periodic administration for protection against newer strains.

9 COVID-19 waves and reinfections

The COVID-19 waves can be described as curve of infections that develop during a pandemic, the number of infections rises and then drops; this every cycle is one "wave" of COVID-19. The exact cause of Coronavirus wave is unknown, however it has afflicted a number of nations including Kyrgyzstan, Australia, South Korea, Israel, New Zealand, India, Japan, Spain, United State of America, and United Kingdom. A few new Coronavirus strains, including the UK virus, the South African virus, the B.1.617 variation, and the double mutant form of SARS-CoV-2, may have generated the outbreaks in the United States and the United Kingdom. These Coronavirus mutations are highly contagious and have the ability to evade the human immune system. A recent studies in Denmark found that risk of COVID-19 reinfection is 0.65% (72 of 11,068 tested positive in PCR test again) during the first wave between March and May 2020, while in the

second wave 3.3% (16,819 of 514,271 tested positive in PCR test again) during September to December 2020. The rate of reinfection was five times higher during the second wave as compared with previous COVID-19 infections (Hansen et al., 2021).

10 Herd immunity and COVID-19 reinfection

Herd immunity is a public health terminology to describe the notion that when an adequate public in a society have immunity from Coronavirus, then society will be protected from the outbreak of that disease. This can happen either because these people got vaccinated or had already been infected and have developed protective antibodies against future infection. The theory of herd immunity sticks only for same type of virus. However, the theory of herd immunity does not apply to new or mutant variants of the original virus strain because these new variants may bypass or cheat the immune system. At present, thousands of new virus variants are available, so herd immunity could not provide protection from different types of virus variants.

11 Prevention against COVID-19 reinfection

The possibility of reinfection also depends on the chances of re-exposure to infectious cases of COVID-19. The increased transmission of the COVID-19 virus also increases the possibility that reinfections may occur. A recent population level observational study in Denmark assessed the protection against reinfection with SARS-CoV-2 and found that a first infection with COVID-19 provides only 47% protection against a COVID-19 reinfection for elder person (65 years and over), compared with 80% protection across all age groups. The study also found that the level of protection against reinfection stayed stable for more than six months. These outcomes highlight the importance of physical distancing and vaccinations, even among those who have already had COVID-19 (Hansen et al., 2021). The following preventive measures for COVID-19 infection are suggested as main approach during this pandemic.

1. Strict obedience to COVID-19-appropriate behavior (CAB), i.e., in public settings, wear a mask and keep a distance of about 6 ft from other individuals wash your hands, restrict your travel, avoid eating or drinking in public places, avoid crowds and confined spaces, and self-quarantine, if sick.

2. Deep, extensive, rapid and real-time whole-genome sequencing studies are required to recognize new mutations and variants of concern to provide valuable information regarding growth, functioning, transmission capacities, and mutation of organisms. This information can be applied to diagnosis, control, treatment, and development of vaccines.
3. COVID-19 vaccinations offer a higher grade of immunity, a greater number of antibodies, and a longer duration of protective immunity than spontaneous infection with SARS-CoV-2. Increased immunization rates are critical for limiting the severity of reinfection. However, the vaccination is not a full assurance for protection against reinfection so the person should be obedient to CAB.

12 Implication on COVID-19 reinfection studies

COVID-19 reinfection has been reported all across the world and it is noteworthy that it can occur with or without changes in the virus's spike protein. The rate of reinfection was five times higher during the second wave as compared with previous COVID-19 infections. The risk of reinfection with delta variant (B.1.617.2) is 46% higher than the Alpha variant. Asymptomatic or mildly symptomatic patients, immune impaired people, diabetic patients, thyroid disease patients, obese people, frontline and healthcare professionals are all at increased risk of COVID-19 reinfection.

The present work suggests several implications for possible control of COVID-19 reinfection in the society and may guide the future research in this field are as follows: (a) The management of reinfection should be the same as the treatment of the first COVID-19 infection. (b) Strict adherence to COVID-19-appropriate behavior to avoid reinfection with COVID-19. (c) The medical history of patients should be considered, while treating the COVID-19-reinfected cases. (d) The majority of the COVID-19 reinfection cases are due to novel variant of viruses while few are without mutated virus. Thus deep, extensive, rapid and real-time whole-genome sequencing studies are required to estimate the real numbers of reinfections and treat them accordingly with modified the management/therapeutic strategies. (e) The vaccination against COVID-19 has been established as a proven approach for reducing the risk of reinfection. The vaccination leads to diminished transmission of SARS-CoV-2 (and its new variants also) infection in the society, thus an increased rate of vaccination drive would be crucial to control the severity of re-infection.

13 Conclusion

The accelerated spread of COVID-19 disease has created noteworthy challenges for the economies and healthcare systems of the world. The condition has advanced very rapidly and, till date, there is a high degree of ambiguity about the future consequences of the pandemic (Malkov, 2020). A person recovered from COVID-19, may again get infected with COVID-19 after a time interval due to reactivation of virus in patients bodies or attack of genetically different mutant virus is known as COVID-19 reinfection. The COVID-19 reinfection cases were reported by researchers in various regions, more importantly these are asymptomatic or mild, lack of surveillance and genomic sequencing studies make it difficult to estimate the real numbers of reinfections. Both times COVID-19 patients were infected with the viruses; they had differences in some of their genes caused by antigenic drift, antigenic shift, and recombination, known as natural mutations. The world's first COVID-19 reinfection was documented/confirmed in Hong Kong on August 24, 2020, currently, 78 cases, 03 deaths, 56 recovered patients have been reported along with more than 40,000 suspected cases and more than 100 deaths being reinfected with COVID-19. The various scientific reports indicate that the reinfection with COVID-19 occurred due to new variant of viruses, while few are without any mutations. Exposure to SARS-CoV-2 variant virus strains in the future may increase the likelihood of reinfection since the immune system is not sensitive to them. Therefore, genome sequencing of SARS-CoV-2 is necessary to understand why this virus is behaving differently.

The immune system T cells ($CD4^+$ T cell, $CD8^+$ T cell), B cells and antibody responses protect the person from reinfection for some time, but as the time spent immunity fades up, leaving us more susceptible to the Coronavirus reinfections. The COVID-19 reinfection arises several questions for the developers of COVID-19 vaccines, i.e., efficacy of genetically different stain and mutant viruses, durability of immunity and safety. At present, number of cases have been reported who have been vaccinated but get suffered from COVID-19 disease, indicating that the existing vaccines do not provide protection against infection, while it protect against the person from the severity of next COVID-19 infection, if it occurs. Recent research indicates that infection with COVID-19 may not completely protect children and adolescents from reinfection, and immunization is still required to enhance immune responses, prevent reinfection, and decrease transmission. The risk of

COVID-19 reinfection was 0.65% during the first wave, while it was 3.3% in the second wave. It could be stated that the rate of reinfection has increased during the second wave. The management of reinfection should be in accordance with the treatment of the first COVID-19 infection. The strict obedience to COVID-19 appropriate behavior, deep, extensive, rapid and real-time whole-genome sequencing studies and an increased rate of vaccination drive would be crucial to controlling the severity of re-infection.

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