QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SARS-COV-2 REINFECTION

BY

NOUR WALEED ALHUSSAINI

A Thesis Submitted to

the College of Health Sciences

in Partial Fulfillment of the Requirements for the Degree of

Master of Public Health

January 2022

COMMITTEE PAGE

The members of the Committee approve the Thesis of
Nour Waleed Alhussaini defended on 01/12/2021.

_____
Manar E. Abdel-Rahman
Thesis Supervisor

_____
Elmoubashar Farag
Thesis Co-supervisor

Approved:

_____
Hanan Abdul Rahim, Dean, College of Health Science

ABSTRACT

ALHUSSAINI, NOUR, W., Master of Public Health : January : 2022, Public Health

Title: SARS-CoV-2 Reinfection

Supervisor of Thesis: Manar, E, Abdel-Rahman.

Background: SARS-CoV-2 reinfection investigation is on rise, and despite the fact that reviews and studies have attempted to study and define reinfection, none have compared it with all documented conditions in the literature. Therefore, in the quest to better understand COVID-19, this study aims to develop assessment criteria for SARS-CoV-2 reinfection and distinguish other post COVID-19 conditions based on a scoping review, and further study characteristics of reinfected cases in Qatar through a cross-sectional study.

Methods: A scoping review of SARS-CoV-2 reinfection was performed and was reported using the PRISMA-ScR checklist. Eight electronic databases were searched from inception to June 2021, and studies where selected based on a priori identified inclusion criteria. Outcomes compared with reinfection were reactivation, relapse, recurrence, repositive, and persistence. A cross sectional study was further conducted to study characteristics of reinfected cases in Qatar between March and June 2021, intending to use the developed criteria. Univariate and multivariable logistic regression and ordinal logistic regression models were utilized for studying the association between preventive and risk practices with symptomatic status of reinfection and time interval until reinfection.

Results: A total of 96 studies were included in the scoping review. Published evidence varied in the used definition for reinfection while others did not use any. Other post COVID-19 conditions (persistence, relapse, recurrence, reactivation, repositive) were mainly distinguished from reinfection in terms of age, asymptomatic status, time

interval, and seroconversion. The key findings in determining SARS-CoV-2 reinfection are occurrence of reinfection after ≥3 months with at least three negative PCR tests for a confirmed recovery to ensure viral clearance. Subsequently in Qatar, 411 reinfected cases (0.73%) were identified after least 90 days from the first infection. Always performing all combined preventive practices (wearing masks, social distancing, and hand hygiene) had a significant inverse association with symptomatic status of reinfection (adjusted prevalence odds ratio (aPOR)= 0.41, 95% CI= 0.24,0.72, P= 0.002), while engaging in some or all risk practices (physical contact and attending social gatherings) had a significant positive association with symptomatic status of reinfection (aPOR= 1.94, 95% CI= 1.21,3.12, P= 0.006). Combined preventive practices was borderline associated with longest time interval (>332 days) until reinfection (aOR=1.57, 95% CI= 1.00,2.48, P=0.051), however, risk practices showed insignificant association with shorter time interval to reinfection (<275 days) (aOR= 0.81, 95% CI= 0.55,1.20, P= 0.291).

Conclusion: The findings will help in development of guidelines and implementation of strategies for global public health measures, thereby assisting in impeding the spread of the virus.

DEDICATION

I dedicate this thesis to my beautiful parents, who provided endless amount of motivation and for always being there with love, care, and patience. To my twin brother and two sisters for their immeasurable encouragement and continued support. To Noor Hamad, my friend and colleague for her continuous encouraging remarks.

ACKNOWLEDGMENTS

All praise is due to Allah, the Lord of all Worlds, the Beneficent, the Merciful.

I would like to thank my primary supervisor, Dr. Manar Elhassan for her years of commitment, guiding my learning to inquire and find meaning through research and positioning me to grow my inner strength in the process of seeking new knowledge.

I also wish to acknowledge Dr Elmoubashar Farag, Acting Head of Communicable Disease Control Programs at MoPH, for his co-supervision, guidance, and support. Special thanks are extended to Ms. Esraa Yassin, Public Health Coordinator at the MoPH, for her support. I would also like to thank Ms. Yousra Ziyada, Case Investigator at the MoPH for her constant help and unwavering support.

I would like to extend my sincere thanks to the examiners for their valuable inputs that were included in this thesis and for their generous time spent providing guidance, encouragement, suggestions, and comments.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

COVID-19	Coronavirus disease 2019
WHO	World health organization
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
IBV	Infectious bronchitis virus
CoV	Coronavirus
HCoV	Human coronavirus
MERS	Middle East respiratory syndrome
SARS	Severe acute respiratory syndrome
USA	United States of America
UK	United Kingdom
RT-PCR	Reverse transcription polymerase chain reaction
NIH	National institute of health
PRISMA-ScR	Preferred reporting items for systematic reviews and meta-analyses extension for scoping review
MeSh term	Medical Subject Headings
NCO	Newcastle-Ottawa tool
HCWs	Healthcare workers
AMR	The Americas region
WPR	West pacific region
EUR	European region
EMR	East Mediterranean region
SEAR	Southeast Asian region
AR	African region
CDC	Centers for disease control and prevention

WGS	Whole genome sequencing
NA	Not applicable
NR	Not reported
NP	Not performed
NS	Not specified
VOC	Variant of concern
VOI	Variant of interest
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
CT scan	Computerized tomography scan
MoPH	Ministry of Public Health
VIF	Variance inflation factor
DAG	Directed acyclic graph
AIC	Akaike information criteria
BIC	Bayesian information criteria
POR	Prevalence odds ratio
OR	Odds ratio
CI	Confidence intervals
IRB	Institutional review board

CHAPTER 1: INTRODUCTION

Background

The COVID-19 pandemic has triggered a massive public health crisis, leading to illness, death, economic devastation, and a shortage of healthcare workers [1]. Cases of unknown pneumonia were first reported in Wuhan, Hubei, China in December 2019, and thus declared by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) pandemic on March 11, 2020 [2]. Reinfection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has only recently become apparent; however, different studies employ different case definitions, making comparisons difficult. Furthermore, there is a dearth of epidemiological research on the description of reinfected cases in the Arab world. Our study builds upon these limitations and aims to identify assessment criteria for SARS-CoV-2 reinfection from the literature and complement findings through a descriptive analysis of characteristics on reinfected cases in Qatar.

Thesis structure

This thesis consists of two interrelated parts. The first part is a scoping review used to assess criteria for defining SARS-COV-2 reinfection. This scoping review provides a solid foundation for this thesis by conceptually mapping a definition of SARS-COV-2 reinfection that can contribute to guide clinicians in diagnosis of confirmed reinfected cases and sample selection in data analysis studies. The second part of this thesis is a cross-sectional study on SARS-COV-2 reinfection in Qatar intended to use the SARS-COV-2 reinfection criteria-developed in the first part based on available data as complementary for findings in the scoping review and for describing characteristics of reinfected cases and also explore associations of preventive and risk practices with symptomatic status of reinfection and time interval

between the first and second infections in the State of Qatar.

CHAPTER 2: REVIEW OF THE LITERATURE

Coronavirus evolution

Avian infectious bronchitis virus (IBV, the first coronavirus, was discovered by Beaudette and Hudson in 1937 [3]. The term coronavirus (CoV) is derived from the Latin word "corona," which means "crown" and refers to the glycoprotein spikes of these viruses when viewed through an electron microscope [3]. CoVs were first discovered in domestic and lab animals before being noticed in humans. In the 1960s, human coronaviruses (HCoVs) were found in a specimen of a boy with a common cold, and the virus was discovered to resemble avian IBVs. Coronavirus genus was later defined [4]. CoVs were classified by the International Committee on Taxonomy of Viruses (ICT) as belonging to the family Coronaviridae and the order Nidovirales, as well as the Coronaviridae subfamily comprises of toroviruses and coronaviruses. The CoVs were further divided into four genera: the alpha, beta, gamma, and delta CoVs (Figure 1). Alpha and beta CoVs are known to infect humans. CoVs is a large virus family that can be found in a variety of animals, including bats, cats, camels, and cattle. Animal CoVs can infect humans on a rare occasion, therefore consequently causing epidemics like Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and COVID-19, which can spread among humans and are caused by Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2 viruses, respectively [5-8]. All three viruses belong to the beta coronaviruses [9-11].

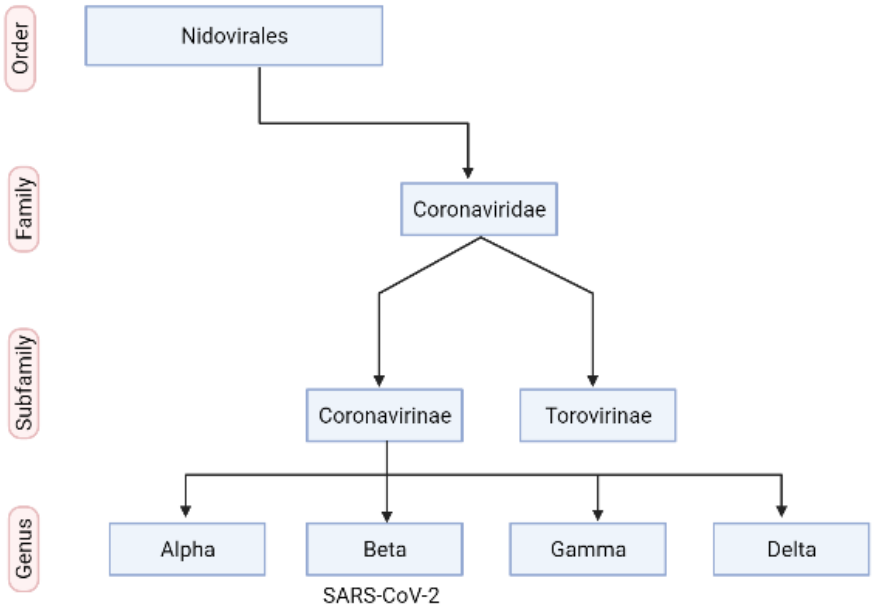

Figure 1. Taxonomy of coronaviridae according to the international committee on taxonomy of viruses.

Note: Created using biorender.com.

SARS-CoV-2 virus

A novel coronavirus emerged in Wuhan, the capital city of Hubei province of China in December 2019 as few patients who had an unknown cause of fever and symptoms of lower respiratory tract infections were detected [12]. The newly discovered virus was initially named 2019 novel coronavirus (2019-nCoV) in January 2020 and then was officially termed COVID-19 in February 2020 by the World Health Organization [13]. For the last twenty years, COVID-19 is the third significant outbreak for coronavirus which overwhelmingly surpassed previous CoV disease outbreaks (SARS and MERS) in the spread of the disease [14]. Therefore, the WHO declared COVID-19 pandemic in March 2020 after investigating the transmissibility and severity of the virus [15]. Understanding the epidemiology of this disease allow us to understand the natural history and burden of it, along with how it impact different communities [16].

Epidemiology of COVID-19 pandemic

The spread of COVID-19 posed an enormous threat to public health globally reaching more than 230 million confirmed cases and exceeding 4.8 million deaths as of October 2021 [17]. According to the WHO region classification, the Americas and European regions have the highest number of cases surpassing 91 and 72 million cases respectively. Cases in the East Mediterranean region reached more than 16 million cases in October 2021 [17]. The least in the African region reaching 5.5 million in August 2021 [17].

There has been a wide range of impacts due to the COVID-19 pandemic in nations around the world, from countries like the United States of America (USA), United Kingdom (UK), and Turkey with high infection and high mortality rates to countries like Australia with lower rates [18]. Possible reasons for such variation were addressed by researches as due to age distribution in countries, genetic predisposition, strict preventive measures, and better healthcare systems [19]. Researchers have identified an array of variables that act as risk factors for developing a severe or fatal COVID-19 course of a disease. These factors include higher age, male gender, post menopause, history of comorbidities including hypertension, diabetes, and cardiovascular diseases [20]. For the modifiable factors, certain mitigation measurements can be applied to reduce or eliminate the impact of the virus [21].

Ever since the beginning of the pandemic, global efforts have been devoted to developing several and different public health measures to reduce or delay the transmission of the virus. Such efforts included interventions at multiple levels in the community, ranging from individual to country-level. As part of primary prevention, at the individual level, strategies include personal protection like hygiene, cleaning, safe food handling, and social distancing [22]. Other measures that included governmental involvement and country level interventions such as wearing masks in public areas,

imposing social distancing, banning social gatherings, restricting traveling, isolating infected cases, contact tracing, and quarantine contacts for the aim of detecting cases as early as possible to prevent reoccurrence of outbreaks [23, 24]. Another avenue being pursued to ameliorate the spread and severe effects of COVID-19 is the use of vaccination [25].

The global drive to vaccinate the highest number of populations against SARS-CoV-2 began in December 2020 with countries in the Middle East, Europe, and North America directing the implementation of mass immunization campaigns [26]. The major types of vaccines against SARS-CoV-2 being used across multiple countries and have also met the WHO criteria for safety and efficacy after evaluating each are Oxford/AstraZeneca, Pfizer/BioNTech, Moderna, Sinopharm, and Janssen [27].

COVID-19 in Qatar

Qatar has suffered a large SARS-CoV-2 outbreak, however, since the peak, there has been a dramatic decrease in the number of cases [28] until the start of the second wave in March 2021 [29]. The number of cases in Qatar reached more than 240 thousand cases and 611 deaths as of November 2021 [17]. Since the beginning of the outbreak, Qatar government have been rapidly acting to combat the spread of the virus including imposing stringent public health measures such as limiting on travel, closure of borders, schools, non-essential businesses, suspension of mass gatherings, and instituting a partial lockdown [30]. Individual preventive measures imposed in the country included wearing masks in public and maintaining social distance of at least one meter [30]. The infection in Qatar has been distinguished by its low case, illness severity, and death rates [28]. Such low rates may be attributed to well-structured and well-coordinated healthcare services, the deployment of a comprehensive public health response, and the construction of the National Health Response to COVID-

19 governance structure for rapid decision making [31]. While the top priority is to prevent or treat infected cases, understanding the impact of the pandemic gives opportunity to manage and restore social and economic welfare [32].

Impact of COVID-19 pandemic

It is imperative to address aspects and consequences of significant catastrophic epidemics that have transformed the globe and introduced new policies and public health measures to bear successful interventions for controlling them. Such impacts include the precipitation of community and nosocomial transmission which might lead to an increase in rates of morbidity and mortality in communities and in healthcare settings [33]. New SARS-CoV-2 variants were found be more contagious and cause severe illnesses [34], as this might lead to continuous outbreaks and pose a serious public health concern [35].

Not only is the COVID-19 pandemic a threat to people's physical health; it is also affecting their mental health [36]. This pandemic has steered so much fear and uncertainty among the public leaving a psychological negative impact such as stress, anxiety, and even depression [37]. Furthermore, isolating infected or those in contact with cases from their relatives and friends provide them with a sense of loss of freedom in addition to the anxious feelings of the disease's possibility [38]. Loss of opportunities, social exclusion, and experiencing death of a family member who was affected by COVID-19 are all potential sources that could upsurge mental distortions [36].

Additionally, due to the preventive measures implemented in many countries to combat the spread of the virus, such impediments may exacerbate the impact of individual’s and country’s economic systems [39]. Therefore, financial loss could be reached as a result of reduction in transportation/travel between or within countries leading to less tourism [40]. Other reasons could be trade-related, such as a reduction

in consumption of goods and services due to lockdown measures, as well as lack of foreign exchange which might affect the country's economic growth due to governments enforcing restrictions on foreigner entries to countries [35].

In addition to the enormous load that have been put on health-care systems during COVID-19 pandemic, those with chronic diseases were also unable to receive the support they need due to lack of access to health services during the waves, as they may require ongoing routine care [41]. As the impact of the pandemic is addressed, further understanding of the clinical manifestations of infected patients is essential so that resources can be allocated to the prevention and treatment to those who catch the disease.

Clinical presentation of COVID-19 patients

COVID-19 mainly affects respiratory system [42]. Clinical manifestations have revealed high variability among COVID-19 patients. While some patients hold an asymptomatic disease [43], the predominant symptoms of COVID-19 patients are fever, dry cough, and fatigue and other less common symptoms are sore throat, headache, loss of taste or smell, muscle pain, nausea, vomiting, chills, diarrhea, nasal conjunction, and skin rash [15]. Difficulties in breathing is an indication of probable pneumonia and necessitates immediate clinical attention and care [44]. According to WHO severity classification [45], pneumonia symptoms are found to be related to moderate and severe clinical course. A string of these symptoms merely rarely leads to a diagnosis, as other diagnostic methods shall be used [46].

Diagnostic methods

Several multiple diagnostic tests have been developed for the identification of COVID-19 patients rapidly and accurately [47]. The following categories describe the most commonly used methods for detecting patients with COVID-19:

Nucleic acid-based tests

For the detection of SARS-CoV-2 and the control of outbreaks in communities, accurate and rapid diagnosis is essential. Nucleic acid amplification techniques (NAATs), using reverse transcriptase polymerase chain reaction (RT-PCR), can be utilized as the primary diagnostic tool for SARS-CoV-2. The World Health Organization (WHO) published guidelines for laboratory testing of suspected patients with COVID-19 which recommended collecting specimens from the upper respiratory tract (URT) using RT-PCR [48]. This test can help identify the RNA sequences that make up the virus' genetic material. There are multiple other methods used for amplifying the nucleic acids and detecting the virus [49].

Although RT-PCR is the gold method used for detecting COVID-19 [50], it is important to note that its results are dependent on the specimen collected, which may have flaws, including the chance of getting false negative results that occur as a result of single tests, errors in sample collection, machine handling, and incorrect interpretation of the results [51, 52]. Therefore, further detecting methods may be required to confirm the infection [53].

Serologic tests

Detection of anti–SARS–CoV–2 antibodies could indicate that a person is infected with COVID–19 specifically in case of false-negative/positive results. In order to evaluate immunological response, antibodies in serum are usually used. These assays are based on enzyme immunoassays, which detect the presence of virus-specific antibodies in the blood, or on live or pseudo-virus neutralization assays, which detect functional neutralizing antibodies. Enzyme-linked immunosorbent assay (ELISA) is the most used technique for detecting specific SARS–CoV–2 antibodies as it permits researchers to acquire specific and sensitive results in as little as from one to five hours [54-57]. Serological tests are critical in determining the existence of antibodies that

indicate a protective immune response [58].

Other diagnostic tests

Computed tomography (CT) scan and chest radiography (CXR) are two other less time-consuming methods for detecting the presence of viral pneumonia. Chest X-ray and CT scan are endorsed as the first-line diagnostic tool for COVID-19 in multiple countries [59] due to their usefulness, lower cost, and availability [60]. However, these methods are of less value when the infected is with an early or mild course of the disease [61].

Multiple other methods are developed for rapid and low-cost testing procedures to conduct comprehensive surveillance programs [62]. Several aspects should be examined when choosing the best diagnostic test. Although the sensitivity and specificity rates are crucial for diagnostic tools; however, they are not the only factors to consider. Indeed, in cases of pandemics, an effective test should be quick, repeatable, available, and affordable to perform multiple times on a significant proportion of the population [63]. Hence, selecting the right diagnostic tool depends on the purpose of the investigation whether clinical or epidemiological tracing systems [63].

SARS-CoV-2 variants

When a virus infects a human, it attaches to the cells, enters them, and replicates its RNA, allowing it to spread. If a copying error occurs, the RNA is altered. These alterations are described as mutations and viruses with either one or more mutations (change in whole genome sequence) are named variants [64]. When a variant exhibit distinct physical characteristic, it is then referred to as a strain. In other words, a strain is a variant that differs from its reference virus in terms of structure and behavior and such differences include, but not limited to, bindings to a different cell receptor, replicating faster, transmitting more efficiently, disease severity, and vaccine performance [64]. When a variant completely deviates from the parental virus it is to

be recognized as a new lineage, or branch in the phylogenetic trees [65]. Genomic sequencing is a process used to decode the virus's genes and understand different variants circulating around the globe. This method also helps identify SARS-CoV-2 and tracks the evolution of new variants over time, and helps understand how these changes affect the virus's properties and to better understand how it harm human health [66]. The emergence of new variants might lead to serious consequences such as drug resistance and vaccine failure [67], hence possibly causing an increased infection and mortality rates [68].

The appearance of variants that offer greater risk to the public health globally has spurred the WHO to provide labels for each specific variant as either a variant of interest (VOIs) or a variants of concern (VOCs) alongside the scientific terminologies available [69]. A VOI is one that possesses a genetic aptitude that influences virus properties such as disease severity, immunological escape, transmissibility, and diagnostic escape. VOCs tend to be of more highly transmissible, highly increase in disease severity and death compared to VOIs, with higher potential of immune escape, and a considerable decline in the efficacy of vaccinations and treatments [69]. Until now there are four types of VOC and two variants of interest classified by the WHO [69] (Table 1). It is further important to comprehend the immune response when infected with different strains of the virus.

Table 1. Labeled Variants of Concern (VOC) and Variants of Interest (VOI) According to WHO Classification

WHO label	Scientific name	Country
VOC		
Alpha	B.1.1.7	United Kingdom
Beta	B.1.351	South Africa
Gamma	P.1	Brazil
Delta	B.1.617.2	India
VOI		
Lambda	C.37	Peru
Mu	B.1.621	Colombia

COVID-19 immune response

The human body contain two components of the immune system, the innate and the adaptive immune systems [70]. The innate system is the first line defense mechanism against foreign bodies entering the body as it acts quickly. It has only a limited ability to prevent the transmission of pathogens, while the adaptive immune response is responsible for this, though it may be of a slower process compared to the latter, however, provides long-term protection against the pathogen [70]. In the adaptive immunity, diverse classes of antibodies are created to neutralize the infected cells. One of the primary functions of antibodies is to bind to pathogens and prevent them from infecting or entering cells [71]. The production of detectable antibodies in the blood against a specific antigen is known as seroconversion [72].

Individuals infected with the SARS-CoV-2 virus acquire detectable neutralizing antibodies (NAb) and develop IgG seropositivity in 90% to 99% of cases after two to four weeks after the infection [73-78]. NAb levels tend to be lower in individuals with mild or asymptomatic infections than they are in those with more severe disease, and in younger adults and some studies suggest that antibody levels begin to decline after few months of infection [76, 77, 79-81]. IgM is detected usually one to two weeks after infection as high levels are seen in the early stages of illness, while elevated IgG levels are associated with a later stage of infection [82]. When the IgG and IgM are positive,

this indicates a recent infection, while if both are negative, this implies no infection, or no antibodies produced. If IgG was detected with no IgM, this means the patient is in the rehabilitation phase [83]. It is also crucial to note the importance of identifying IgA antibodies since they rise in the early phases of the infection which can be used to detect it at early stages and they also act as the most critical immunoglobulins for fighting pathogenic infections in the respiratory and digestive systems [84, 85]. Fox et al. [86] suggested that the type of immunity developed by IgA, helps in in preventing SARS-CoV-2 infections.

Large studies conducted previously in the USA [87], UK [88], and Denmark [89], illustrated that SARS-CoV-2 infection provided from 80% to 90% protection against reinfection for up to 7 months. In support to these findings, a recent systematic review (pre-print) [90], demonstrated that roughly 90% of those who had been infected with SARS-CoV-2 developed memory cells for the virus, which persist for not less than 6 to 8 months after recovery. On the other hand, some individuals fail to develop antibodies after infection as possible reasons remain unclear [80]. Some particular groups, such as those who are immunosuppressed as a result of medications or who have underlying medical disorders, are likely to be at higher risk of reinfection or persistence of the virus due to a weak immune response to SARS-CoV-2 compared to other healthy individuals. Because of a phenomenon known as antibody-dependent enhancement (ADE), antibodies do not always inhibit virus entry into cells, however, in some cases, they enable the virus to enter cells and amplify the immunological response [91]. All of this may contribute to increased susceptibility to SARS-CoV-2 reinfection.

SARS-CoV-2 reinfection

According to the CDC [92], the simple definition of reinfection is getting infected once, recovering, and then becoming infected again. SARS-CoV-2 reinfection

have been documented in several countries throughout the world [58, 68, 93, 94]. In August 2020, the first case of reinfection was documented in Hong Kong [95]. The time interval between the two episodes for this reinfected case was 4.5 months, with the first infection causing mild symptoms and an asymptomatic course of disease in the second infection. Recovery of the patient was confirmed through two negative PCR tests and confirmed reinfection was determined by whole genome sequencing, which revealed that the two infections were from separate clades/lineages [95]. Other reinfected cases reported in many other regions, such as Pakistan [58], North America [96], Libya [93], Qatar [94], and Japan [97].

By virtue of the evident duration of protection from reinfection following natural infection, several studies reported an increase in reinfected cases [98-100]. Previous infection of SARS-CoV-2 does not guarantee full immunity and full protection from reinfection as the degree and duration of immunity are still not entirely clear. As a result, many studies reported an increase in rate of reinfection and could be due to age, absence of neutralizing antibodies, emergence of new strains which leads to escape the antibodies, or immune response level [95, 101, 102]. Some studies suggest that those who had a first infection with mild symptoms tend to have weaker immunity therefore leading to less protection from a second infection when compared to those with severe illness [103, 104]. However, further investigation and identification of reinfection and risk factors are required. Further comprehensive details on reinfection and reinfected cases are thoroughly studied and covered in the review, Chapter 3.

CHAPTER 3: ASSESSMENT OF SARS-COV-2 REINFECTION AND DISTINGUISHING OTHER POST COVID-19 CONDITIONS: A SCOPING REVIEW

Background

The fast spread of COVID-19 poses substantial concerns for many countries' economies and healthcare systems [105]. Even in this rapidly evolving circumstance, there is still a tremendous degree of uncertainty about the pandemic's potential outcomes. One of the major important questions that remains unresolved is whether persons who recover from COVID-19 can be reinfected with SARS-CoV-2. Moreover, it is also uncertain whether testing positive again will be deemed reinfection or is a result of another cause.

Multiple case reports and studies have been published on retesting positive for COVID-19, and some focusing on reinfection as the main outcome [58, 68, 83, 93]. Several studies are suggestive that SARS-CoV-2 reinfection occurrence is rare accounting for 0.17% [98], 0.3% [87] , 0.47% [106], while other studies showed higher rates accounting for 2.7% [87], 4.5% [107] and even 11.3% [87]. This variance and inconsistency in reinfection rates could be attributed to the lack of a standardized definition, as studies may have utilized different evaluation criteria for a confirmed reinfection and confirmed recovery, and this heterogeneity may result in incomparable results.

We will be able to better understand reinfection if we understand how patients recover. Discharge criteria were created to imply patient recovery. Countries may differ in the use of discharge criteria to confirm recovery from an infection [106, 108]. According to the initial discharge criteria developed by the WHO in January 2020 [109], patients are discharged after having two consecutive negative tests following infection, then this criteria was later revised and updated in May 2020 to require patients

to spend 10 days in isolation after symptom onset, in addition to at least 3 days without symptoms (including without fever and without respiratory symptoms), asymptomatic cases are to be isolated only for 10 days after a positive PCR test [110]. Additionally, the Cycle threshold (Ct) value is used sometimes for confirming recovery as being part of discharge criteria. Some places regard a Ct value of fewer than 30 to be a positive case [111], while others consider a threshold values of less than 35 [112], 37 [113, 114], 38 [81], or 40 [115] to be considered as a positive case infected with COVID-19. This variation in the determined cutoff could be owing to a predefined cutoff value for certain tests used, or it could be related to the test's last cycle [116].

Retesting positive is a broad term that can refer to one of a variety of different mechanisms. It is imperative to note that these mechanisms might occur rather than reinfection, and each should be clarified for accurate findings and interpretation of results. Such mechanisms include SARS-CoV-2 *persistence*, SARS-CoV-2 *reactivation*, *relapse* of COVID-19, *repositive* test, and *recurrence* of COVID-19. Several studies confuse these terminologies with reinfection, therefore, leading to incorrect interpretation of findings. These mechanisms will be referred to as "post COVID-19 conditions" in this research. *Persistence* of the virus is when the virus is not cleared, although instead, remains in specific cells of infected people [117]. History of comorbidities and the development of a critical condition when infected are two factors that may delay virus clearance and lead to its persistence in the body [118]. *Reactivation* of a virus is a process where a latent virus which infected a host cell switches to a lytic stage of replication, allowing the virus to spread. This mechanism has been linked to a variety of stressors, including infection with another virus, physical changes (such as fever, menstruation, and sunlight exposure), nerve trauma, and immunosuppression [119]. *Relapse* of a disease is referred to the return of signs and symptoms of a disease

after remission [120]. Moreover, it was stated before that *recurrence* of a disease occurs due to persistence of a virus, relapse of the disease, reactivation of the virus, or reinfection with a new strain [121-123]. *Repositive* refers to a patient who got re-tested positive due to findings a nucleic acid in the body after recovering from COVID-19 [124]. Some studies were conducted on these post COVID-19 conditions and definitions were developed for a few of them.

Regardless of the fact that some studies have been conducted and investigated reinfection and possibly attempted to define reinfection, none have yet discussed and presented reinfection in relation to all other possible post COVID-19 conditions. Therefore, this study aims to provide assessment criteria and propose definitions for reinfection and the other conditions.

Aim and objectives

Aim

Propose assessment criteria for defining reinfection in recovered COVID-19 patients

Objectives

- Identify criteria used for defining SARS-CoV-2 reinfection in the literature;
- Examine the epidemiological, diagnostic, and clinical features in the literature that characterize SARS-CoV-2 reinfection;
- Conceptually map the literature according to different post COVID-19 conditions confused with reinfection;
- Map out the range of variables and tests used to define SARS-CoV-2 reinfection and other post COVID-19 conditions and develop formal definitions;
- Identify gaps and areas for future research that require better understanding of SARS-CoV-2 reinfection.

Methods

Study design

In this study, a scoping review was used, which is defined as a type of research that aims to "map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research" [125]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping review (PRISMA-ScR) guideline was used for reporting this study [126].

Study eligibility criteria

Inclusion criteria

- *Study design:* All types of epidemiological studies were included in this review with no restrictions.

- *Participants:* Patients who had recovered from an episode of SARS-CoV-2 infection, thereafter, tested positive again for COVID-19. To eliminate the possibility of including cases with prolonged positivity, we included only cases which had a laboratory confirmed negative test between the two positive tests for SARS-CoV-2. This was in accordance with the CDC's recommendation as the prolonged positive PCR for 90-day time after initial infection represents persistence of the virus rather than a true reinfection with COVID-19 [127].

- *Outcome*: Studies considering reinfection as an outcome or any of the following post COVID-19 conditions which are often confused with reinfection: recurrence, repositive, relapse, late presentation, delayed presentation, persistence, or reactivation. These terms were determined a priori in a preliminary search before conducting the scoping review and were chosen as they were commonly used and reported by several researchers.

- *Time*: All articles published since inception of COVID-19 pandemic in 2019

- Only full text, peer-reviewed articles published in English were included

Exclusion criteria

- Articles on coronaviruses in general, with no emphasis on the novel COVID-19
- Research describing non-human studies, such as articles focusing on animals
- Review studies since the emphasis was on evaluated individual cases
- Non-confirmed or doubtfulness of the outcome (e.g. reinfection or relapse)

Data sources and search strategy

Electronic searches

A systematic search and reporting in accordance with the PRISMA 2020 flow diagram [128] was conducted on PubMed, Embase, Cochrane library, SCOPUS, Web of Science, MEDLINE, Oxford Academic, and Wiley Online Library databases between the inception of the pandemic, until 4th of June 2021. As the search method was tailored to specific requirements depending on the database searched, a comprehensive search strategy was developed to capture all articles that addressed SARS-CoV-2 reinfection (Appendix A: Table A 1). The search strategy included all possible synonyms of three main strings which are “COVID-19”, “reinfection”, and “diagnostic methods”. Each synonym was operated with OR Boolean, while each string was operated with AND Boolean. The "Coronavirus" MeSH term was used in Pubmed, while the Embase database used the entrée "coronavirus disease 2019." We limited the search from December 2019 onwards. Multiple keywords were used in the search strategy and are presented in Table 2.

Table 2. Keywords Used in The Search Strategy

COVID-19	Conditions	Diagnostic methodology
COVID-19	Reinfection	Whole genome
Covid19	Re-infection	Sequencing
Corona virus	Re-positive	Seroconversion
SARS-CoV-2	Repositive	Sero-conversion
Severe acute respiratory	Relapse	Antibody response
syndrome coronavirus 2	Recurrence	Immune response
2019nCoV	Recurrent	Viral strain
2019 nCoV	Late presentation	Viral clade
2019-nCoV	Delayed presentation	Variant
HCoV-19	Retested positive	
Coronavirus	Re-tested positive	
Coronavirus disease 2019	Persistence	
	Reactivation	
	Postinfection	
	Post-infection	

Other search methods

Additional searches were conducted using Google Scholar, and a manual search of reference lists of pertinent reviews identified during screening was performed to capture any missed relevant studies.

Screening and selection of studies

Results of the search strategy retrieved from the abovementioned databases were imported into the bibliographic software EndNoteX9 [129], and duplicates were removed. Duplicate citations that remained were manually removed. A total of 1,873 obtained studies were scrutinized and assessed for eligibility by four investigators. Selected studies were based on the inclusion and exclusion criteria outlined above and then, were divided, and downloaded into two groups in Mendeley software which was used for screening. Two authors (N.A. and Y.E.) were assigned to independently screen the first group of 937 articles, while the other two authors (E.Y. and M.A.) screened articles in group two. After initial screening, all eligible articles were imported into Microsoft Excel 2010, merged, and differences between authors were discussed to

reach consensus in relation to ensuring the accuracy of the selection phase. Later, the articles were then subjected to a second round of screening, which included more author discussions. Reasons of exclusion were: no evidence of a negative test between the two episodes, review studies, unpublished articles/ preprints, insufficient information, and non-confirmed cases. The PRISMA flowchart [130] was used to record the inclusion and exclusion of studies (Figure 2).

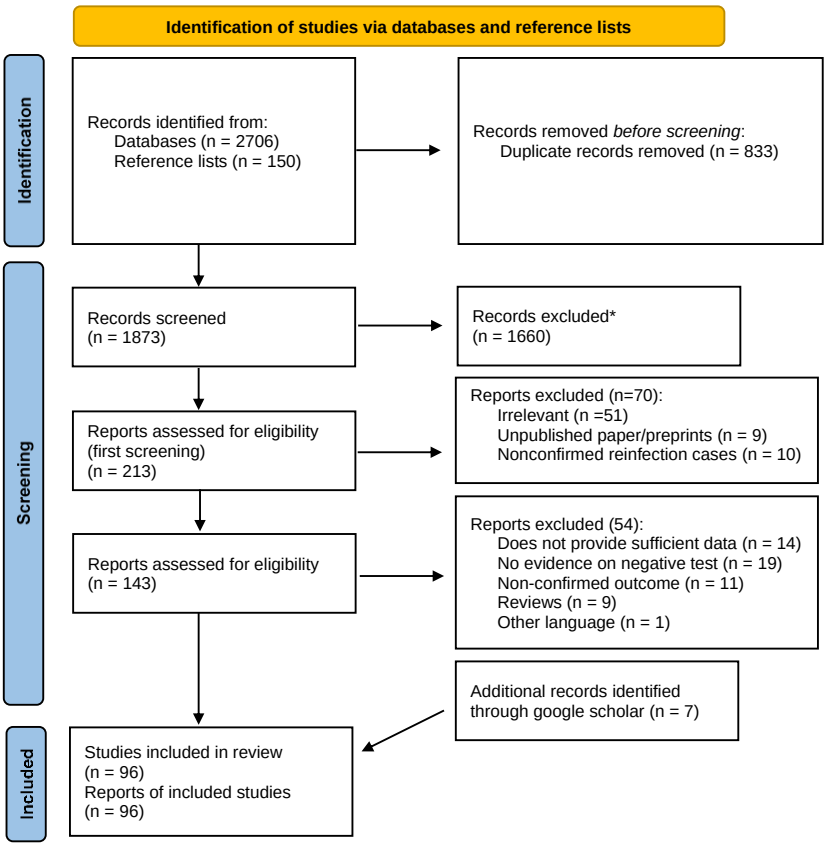

Figure 2. PRISMA flowchart of recorded studies.

Data charting

Studies deemed relevant were procured for full text and data extraction was performed in a pre-defined data extraction spreadsheet. All studies were analyzed and prepared with basic information charted including author, title, study location, study design, number of cases, socio-demographics (age, gender, occupation), patient information (COVID-19 symptoms and comorbidities), reason for detection, method of

detection, exposure information, number of negative tests between the two positives, time interval between the initial and reinfections, vaccination status, whole genome sequencing (if performed), and conclusions of studies. Severity of symptoms was documented based on the WHO classification of symptom severity (Table A 2) [131]. Each author independently charted an assigned part, and a flip technique was used as each two authors flipped parts and re-extracted data. One reviewer (N.A.) merged all extracted data into one table and re-checked the extraction data to ensure the accuracy of reported information.

Quality assessment

The current review, which is based on the development of criteria for defining SARS-CoV-2 reinfection, calls for low-quality studies to be excluded from the study. Thus, quality assessment was performed by groups of three authors for the sake of evaluating the included studies. Case reports and case series were evaluated using the National Institute of Health (NIH) tool which consists of nine questions [132]. The question about whether there was a clear description of the intervention was excluded because it was irrelevant to the goals of the studies that were included. Each question was answered simply with a "yes" or "no," with irrelevant questions labeled "not applicable (N/A)." The NIH tool was scored by counting the number of questions that were answered “yes,” with a total score of zero and a maximum of eight. For observational studies, the Newcastle-Ottawa scale (NOS) was used [133], which has three main domains: selection, comparability, and outcomes. Each observational study was given a score ranging from 0 to 9. The quality of case series/reports and cohort studies was graded on a scale of 0-3 for poor quality, 4-6 for fair quality, and 7-9 for good quality. Some of the domains for granting a score (e.g. regression modeling and adjusting for confounders) were not applicable in cross-sectional studies, so they

were removed from the final assessment scoring, resulting in a different scoring threshold for cross-sectional studies: 0-1 indicated poor quality, 2-3 fair, and above 3 good. For each included study, a final judgment on the quality of the research was made and reported.

Synthesis of results

Data was compiled in the form of tables and graphs, with demographics presented as frequencies and percentages, as well as median and/or ranges as appropriate, in descriptive statistics. Furthermore, definitions were proposed, and data was classified based on each post COVID-19 condition for further comparison with reinfection, and findings were reported accordingly. The main categories for developing reinfection assessment criteria were identified.

Results

Characteristics of included studies

The database search yielded a total of 2,706 studies between December 2019 and June 2021. Following duplicate removal, 1,873 remained for screening, of which 213 were found relevant after the initial screening of titles and abstracts. Of them, 143 were found to be eligible and met the inclusion criteria outlined. Secondary screening and author discussion were conducted to further refine the search, and 96 studies were included [68, 83, 134-227] (Figure 2).

The post COVID-19 conditions included as part of the results of this scoping review were reported as stated in the selected studies. Most studies included cases of reinfection (50/96) as the main outcome [68, 83, 135, 136, 138, 140-142, 154, 155, 157-164, 166-168, 170-172, 174, 175, 177-179, 183-185, 187, 190, 196, 200-203, 206, 209, 210, 212-216, 219, 222, 225], followed by repositive (21/96) [146-150, 153, 156, 169, 176, 180, 181, 188, 197, 198, 204, 207, 208, 211, 220, 224, 227], recurrence (10/96)

[143, 144, 152, 165, 192, 193, 195, 199, 221, 223], reactivation (7/96) [137, 145, 151, 182, 191, 194, 218], persistence (5/96) [134, 186, 189, 217, 226], and relapse (3/96) [139, 173, 205]. Fifty six articles were case reports [68, 83, 134-137, 139-143, 155, 157, 158, 160, 161, 167, 168, 170, 171, 173-176, 178, 179, 181-187, 190, 192-196, 198-205, 211, 212, 214, 216-219, 222, 226], 18 case series [138, 144, 147, 154, 162, 163, 165, 166, 172, 177, 188, 189, 191, 206, 209, 215, 221, 225] and 22 observational studies [145, 146, 148-153, 156, 159, 164, 169, 180, 197, 207, 208, 210, 213, 220, 223, 224, 227]. The number of studies categorized based upon post COVID-19 conditions and study designs are presented in Table 3.

Table 3. Summary of Included Studies Based on Post COVID-19 Conditions and Study Designs

	Case reports/series	Prospective cohort studies	Retrospective cohort studies	Cross-sectional studies	Total
Reinfection	46	2	-	2	50
Persistence	5	-	-	-	5
Reactivation	5	-	2	-	7
Recurrence	8	1	1	-	10
Relapse	3	-	-	-	3
Repositive	7	4	8	2	21
Total	74	7	11	4	96

The total number of participants for all included articles was 1,071. The rate of females in included studies was slightly higher than males accounting for 55%. Age ranged between three months to 95 years old. Furthermore, 18% of the total population of included studies were healthcare workers (HCWs) and seven of 96 conducted their research exclusively among HCWs [138, 162, 190, 206, 210, 214, 221]. Fifty-four

studies reported having patients with comorbidities prior to SARS-CoV-2 reinfection [68, 134, 136, 137, 140, 141, 143, 144, 147, 150, 152, 154, 157, 159, 161, 163-165, 167, 168, 170, 172, 173, 175, 177, 180-185, 187-189, 191, 192, 194, 198, 199, 202-204, 206, 208, 209, 211, 216-220, 223-225]. All studies used PCR as a primary diagnostic method for detecting reinfection with COVID-19, followed by antibody testing which was performed by 64 studies [68, 83, 134, 136, 137, 139, 141, 142, 146-150, 152, 154-158, 160-163, 165, 170-173, 177-180, 182-189, 193-195, 197, 200, 202, 203, 205-212, 214, 215, 217-219, 223, 225-227], and whole genome sequencing (WGS) was undertaken in 23 studies [68, 134, 142, 154, 155, 157, 159, 160, 166, 170-172, 177-179, 203, 206, 209, 212, 214, 217, 221, 225].

Geographical display of included studies according to WHO regions is presented in Figure 3. Majority of studies were from and the Western Pacific Region (WPR) (31/96) [83, 108, 136, 139, 143, 146-150, 153, 156, 160, 172, 180, 188, 197, 207, 208, 211, 215, 220, 224, 226-229] followed by 26 in the European region (EUR) [68, 134, 155, 157-159, 161, 162, 164, 166, 168, 170, 173, 182, 183, 187, 191, 193-195, 209, 210, 214, 216, 218, 221], 22 in the region of the Americas (AMR) [140-142, 144, 165, 167, 169, 171, 174, 177-179, 181, 184, 192, 199, 200, 202, 203, 206, 217, 219], 9 in the South-East Asian region (SEAR) [135, 137, 138, 154, 163, 198, 204, 213, 222], and 8 in the Eastern Mediterranean Region (EMR) [175, 176, 185, 190, 196, 201, 212, 225]. Most included research articles were clustering in certain areas such as the western part of the EUR, and in certain countries in WPR such as China that was equal to a total of 28 studies [83, 139, 143, 145-153, 156, 160, 180, 186, 189, 197, 205, 207, 208, 211, 215, 220, 223, 224, 226, 227]. Studies on cases of reinfection had been published in all regions except AMR. The WPR articles covered all post COVID-19 conditions, whereas the EUR research focused on all except repositivity. The majority

of the articles in the EMR focused on reinfection, with the exception of one that looked into repositivity. Reinfection, recurrence, persistence, and repositivity were studied in the AMR region, while reinfection, reactivation, and repositivity were studied in the SEAR region. No studies were found in the African region (AFR), in many parts of the EUR, and in some parts of the AMR.

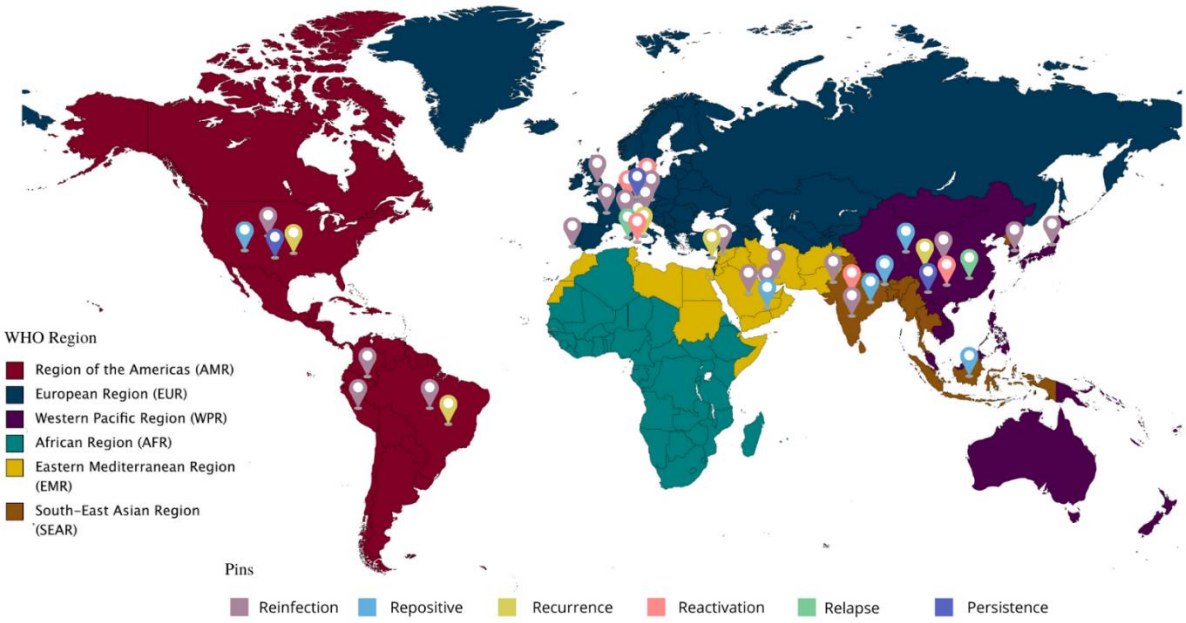

Figure 3. Geographic distribution of included studies based on post COVID-19 conditions.

Main findings of included studies

Table 4 demonstrates findings based upon post COVID-19 conditions. Studies that covered repositive (n=547) and reinfection (n=343) had the highest number of participants. Age ranged widely in all post COVID-19 conditions except persistence, which only included adults and the elderly (range= 44-77 years). Females predominated in all post COVID-19 conditions except persistence, which had a higher proportion of males (62.5%).

Furthermore, 51% of patients with reinfection had more than two negative tests

between the two infections. On the other hand, majority patients who had reactivation of the virus had at least two negative tests until the next positive result accounting for 55.6% and patients who experienced repositive, recurrence, or relapse primarily mainly had two negative tests accounting for 55.5%, 88.3%, and 100%, respectively. The overwhelming majority of patients with a persistent virus only had one negative test (97.5%).

Among all post COVID-19 conditions, reinfected cases had the longest time interval between the two infections, reaching up to 9 months. Findings also revealed that the majority of patients with reinfection (87.4%) had a time span of more than three months, whereas the greatest number of patients with other post COVID-19 conditions had a time span of less than three months until the second positive result (repositive= 100%, persistence= 97.5%, reactivation= 94.4%, relapse= 100%, recurrence= 93.3%). The main reported reasons for the detection of the second positive results among all post COVID-19 condition groups were follow-up and the emergence of symptoms. The cycle threshold was reported and specified in 26 studies and specifically, among 153 cases. Of the 29 reinfected cases who had a reported Ct value, the larger bulk (76%) had Ct value lower than or equal to 30, and one case in each of reactivation and recurrence also had Ct value lower than or equal to 30. One hundred twenty cases (22%) with repositive had reported a specified Ct value for each case, of them, 96.7% had a value of more than 30. One case in each persistence and relapse had a Ct value higher than 30 as well. Furthermore, repositive cases had a reported general cutoff point with no specification for each case. Sixteen percent of repositive cases considered a Ct value less than 37 to be a repositive case, while 4% considered Ct value less than 38, and 17% with Ct value less than 40.

Although most cases among all post COVID-19 conditions groups had mild

symptoms after the second positive result, accounting for 46%, it is significant to mention that a large number were asymptomatic (30.5%), while fewer had moderate (16.5%) and very few suffered severe (5%) or critical (2%) symptoms. Despite the fact that most post COVID-19 conditions had mild symptoms in the second positive result, persistence had most asymptomatic patients (5%). Moreover, more than half of cases with persistence (60%) and recurrence (55.8%) had comorbidities. Further to that, the majority of patients with comorbidities had mild symptoms (41%) and were asymptomatic (29%). A fatal outcome was reported in nearly 1% of all participants, and all of those who died had previous comorbidities, apart from one case who had no clinical conditions while then developed liver complications after reinfection.

As per the diagnostic methods, the standard test, which is PCR, is performed among all cases in all groups. Studies of persistence, relapse, and reinfection mainly reported testing for antibodies with percentages of 100%, 66.7%, and 59.2%, respectively. As for immunology, although IgG and IgM were found in many cases with different post COVID-19 conditions, IgA was detected in only three reinfected cases, while was discovered in 48 repositive cases Although seroconversion was mainly evident in reinfected cases (41.4%), it was only marginally observed in those with recurrent infection (4.2%). WGS was only found to be primarily performed in reinfection-related studies (6.4% of reinfected cases), and in two persistence studies (5% of persistent cases). Similarly, viral culture was also discovered to be done in two studies among 3% of cases with reinfection. Viral culture was determined positive for five reinfected cases with Ct value less than 30, while only one case had a Ct value more than 30. Five case had a negative viral culture indicating a specific fragment of the dead virus genome was amplified with Ct value more than 30.

Table 4. Main Findings Based on Reinfection and Post COVID-19 Conditions

	Reinfection n[§]=343	Repositive n=547	Persistence n=40	Reactivation n=18	Recurrence n=120	Relapse n=3
Demographics						
Age, median (range)	46.5 (3-95 years)	49 (3 months-82 years)	55 (44-77 years)	47 (3 – 84 years)	50 (16-90 years)	57.5 (31-91 years)
Gender						
Males	38%	47%	62.5%	44.4%	45.8%	0%
Females	58%	53%	37.5%	55.6%	54.2%	100%
Other and NR[*]	4%	0%	0%	0%	0%	0%
Epidemiological factors						
Number of negative tests						
One	24.5%	2.5%	97.5%	16.5%	1.7%	0%
Two	10.5%	55.5%	0%	0%	88.3%	100%
At least one	14%	20.8%	0%	27.9%	10%	0%
At least two	0%	20.8%	0%	55.6%	0%	0%
Three or more	51%	0.4%	2.5%	0%	0%	0%
Time frame						
0-3 months	12.6%	100%	97.5%	94.4%	93.3%	100%
3-6 months	29.4%	0%	2.5%	5.6%	6.7%	0%
6-9 months	58%	0%	0%	0%	0%	0%
Reason for testing (second positive)						
Follow up	10.3%	73.8%	7.5%	38.9%	84.2%	0%
Symptoms	5.8%	0.2%	0%	27.8%	10.8%	66.7%
Routine screening	5.8%	0.4%	0%	5.5%	0.8%	0%
Surveillance	1.8%	0%	0%	0%	0%	33.3%
Contact with case	1.7%	0%	0%	0%	4.2%	0%
NR[*]	74.6%	25.6%	92.5%	27.8%	0%	0%
Clinical factors						

	Reinfection n[§]=343	Repositive n=547	Persistence n=40	Reactivation n=18	Recurrence n=120	Relapse n=3
Cycle threshold value (second positive)						
≤30	6.1%	0.73%	0%	5.6%	0.83%	0%
>30	2.3%	21.2%	2.5%	0%	0%	33.3%
NS[**]	58.1%	40.8%	0%	0%	0%	0%
NR[*]	33.5%	37.3%	97.5%	94.4%	99.17%	66.7%
Symptoms (second positive)						
Asymptomatic	32.4%	20.5%	5%	44.4%	20%	0%
Mild	33.5%	34.5%	0%	38.9%	62.5%	66.7%
Moderate	20.1%	11.3%	2.5%	11.1%	4.2%	0%
Severe	2.3%	3.7%	0%	5.6%	12.5%	33.3%
Critical	1.7%	1.1%	0%	0%	0.8%	0%
NS[**]	0%	0%	90%	0%	0%	0%
NR[*]	10%	28.9%	2.5%	0%	0%	0%
Comorbidity rate	16.3%	7.9%	60%	33.3%	55.8%	33.3%
Outcomes						
Recovery rate	97.7%	99.8%	97.5%	89%	99.2%	66.7%
Death rate	2.3%	0.2%	2.5%	5.5%	0.8%	33.3%
NS[**]	0%	0%	0%	5.5%	0%	0%
Detection methods						
RT-PCR	100%	100%	100%	100%	100%	100%
Antibody test	59.2%	39.7%	100%	16.6%	28.3%	66.7%
WGS	6.4%	0%	5%	0%	0%	0%
Viral culture	3%	0%	0%	0%	0%	0%
Seroconversion						
Yes	41.4%	0%	0%	0%	4.2%	0%
No	10.5%	42.2%	95%	22.2%	15%	100%

	Reinfection n[§]=343	Repositive n=547	Persistence n=40	Reactivation n=18	Recurrence n=120	Relapse n=3
NS[**]	0%	12.8%	0%	0%	70.8%	0%
NR[*]	11.4%	0%	5%	0%	0%	0%
NP[***]	36.7%	45%	0%	77.8%	10%	0%

[§] n= represents the sample size of each group

Note: [*]NR: Not reported [**]NS: not specified [***]NP: not performed

All calculations included denominator of the total number of cases for each specific post COVID-19 condition

Definitions for reinfection and other post COVID-19 conditions

Proposed definitions for SARS-CoV-2 reinfection and other post COVID-19 conditions

Based on our findings in the previous section, definitions of SARS-CoV-2 reinfection and other post COVID-19 conditions were developed and presented in **Error! Reference source not found.**. These definitions were created to aid in the d ifferentiation of reinfection from other post COVID-19 conditions that are frequently perplexed with. When generating definitions, categories in variables with the highest percentages were considered to distinguish each condition.

Table 5. Proposed Definitions for SARS-CoV-2 Reinfection and Other Post COVID-19 Conditions

Conditions	Definition
Reinfection	Retesting positive for SARS-CoV-2 via RT-PCR test which presented mainly asymptomatic to mild symptoms with clear seroconversion with time frame not less than 3-months after the onset of the primary infection and mostly in patients in the middle age
Repositive	Retesting positive for SARS-CoV-2 RT-PCR test which presented mainly asymptomatic to mild symptoms with no seroconversion with time frame less than 3-months after the onset of the first positive and mostly in patients in the middle age
Reactivation	Retesting positive for SARS-CoV-2 via RT-PCR test which presented mainly asymptomatic to mild symptoms with no seroconversion with time frame less than 6-months after the onset of the primary episode
Recurrence	Retesting positive for SARS-CoV-2 via RT-PCR test which presented mainly mild or severe symptoms with no seroconversion with time frame less than 6-months after the onset of the primary episode and mostly in patients in the middle age and those with comorbidities
Persistence	Retesting positive for SARS-CoV-2 via RT-PCR test which presented mainly asymptomatic with no seroconversion with time frame less than 6-months after the onset of the primary episode and mostly in elderly age and those with comorbidities
Relapse	Retesting positive for SARS-CoV-2 via RT-PCR test which presented mainly mild or severe symptoms with no seroconversion with time frame less than 3-months after the onset of the primary episode and mostly in patients in the middle age

Summary of post COVID-19 conditions based on time interval

Figure 4 depicts post COVID-19 conditions stratified by the time interval between two positive tests. As displayed, the majority of cases with post COVID-19 conditions occurred within 3-months accounting for 71% of all included cases among all conditions. Only a few cases (9%) with reinfection, persistence, reactivation, and recurrence had a second positive result after 3-months, lasting up to 6-months from the first positive result. On the other hand, only reinfected patients had a time interval between 6 to 9 months. Number of cases with reinfection varied in time-interval until the second infection, with the majority having been infected again after three (29.4%) and six months (58%) (Table 4). In this review, adults comprised the majority of patients across most post COVID-19 conditions with varying time intervals, while elderly patients were overrepresented in cases with persistence (52%) (Figure 4).

In terms of symptoms, the bulk of conditions had asymptomatic to mild symptoms in the first interval during the second positive test, except relapse which had cases with mild (67%) or severe (33%) symptoms. In the second time interval, one case in each persistence and reactivation had moderate and severe symptoms, respectively. Additionally, patients with recurrence in the second time interval mostly had mild (37.5%) or severe (37.5%) symptoms.

As per number of negative tests between the two positive results, in the first time-interval, most patients with reinfection (51.2%) and persistence (97.4%) had one negative test, while patients with repositive (55%), recurrence (94%) and relapse (100%) had mainly two negative tests. Most patients with reactivation (40%) had at least one negative test. Reinfected cases in the second time interval also had one negative test (56%), however, in the third time interval most reinfected cases had not less than two negative tests (82%).

For reason of detection in the first time interval (<3 months), follow up was predominating in all post COVID-19 conditions except patients with relapse who were mainly tested for symptoms onset (67%). Patients with reinfection and with time intervals more than 3-months highlighted that the main reason for testing was primarily for follow up (60%).

While the majority of seroconversion among the three time-intervals were present in reinfected cases, it was observed in only one case in the second interval. Cases with other post COVID-19 conditions exhibited a low rate of seroconversion in the first two time intervals, with one case with recurrence having seroconversion in the second interval. Different strains of infection were primarily found in cases with reinfection of all time intervals, with just a few of those who had reinfection with a similar strain, and all of those with persistent virus experiencing similar strains.

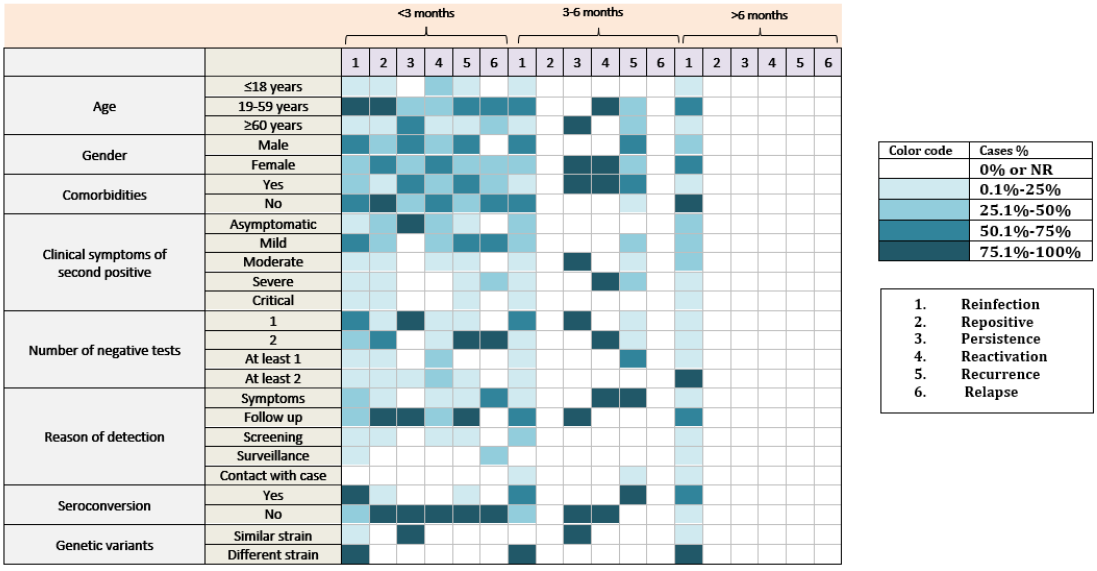

Figure 4 Post COVID-19 conditions stratified based on time interval between two positive tests.

Note: Each condition within each time frame was compared in columns.

For each variable, those with unreported, not mentioned, nonspecified, or not performed variables were eliminated from the denominator.

Persistence and reactivation in the second time interval, included only one case each.

Whole genome sequencing

Seventy-nine cases of who had reinfection and persistence were identified with WGS, as seven cases had similar strains/clades in both infections, while 38 cases were with different strains. WGS was mostly performed in EUR, with 52 cases, while 14 were from AMR, accounting for the majority of cases with WGS performed. Among the seven cases with similar strains, 57% had mild symptoms in the first infection, while 43% had mild and 43% had moderate symptoms in reinfection. Of the two persistent cases with similar strains, one had a virus persisting for less than two months (Ct=35), while the other lasted for more than 4 months. For reinfected cases with similar strains, the time intervals until reinfection were 1.5 month (Ct=19.2, symptoms= mild), 2 months (Ct=36, symptoms= mild), 2.5 months (Ct=35.3, symptoms= moderate), 3 month (Ct=17.8, symptoms= mild), and one case reaching up to 7 months (Ct=not reported, symptoms= moderate). For those with different strains, mild symptoms were predominating in the first and second infections with rates of 76% and 56% respectively. Very few experienced severe symptoms after the second infection in those with different or similar strains. The time interval for reinfected cases with different strains ranged between one to nine months.

Seven of the reinfected cases encountered a variant of concern in the second infection; six of them were with the Alpha (B.1.1.7) lineage and one with the Beta (B.1.1351) lineage. Although several cases had similar symptom status during both infections, only one of the cases who was reinfected with a variant of concern reported similar symptoms. Four cases reinfected with the alpha lineage experienced mild symptoms, one was asymptomatic, and one had moderate symptoms. While in one case, a person who had a beta lineage suffered critical symptoms. The six cases with Alpha lineage were reinfected after one month (Ct=24, 27), 3-months (Ct=31), 8 months (Ct=28), 9 months (Ct=not reported) while the case with beta lineage was reinfected

after 4 months from the first infection (Ct=not reported).

Criteria for assessing SARS-CoV-2 reinfection

Figure 5 demonstrates the proposed assessment criteria for SARS-CoV-2 reinfection, which were developed from findings of this scoping review and are based on the clinical, epidemiological, and diagnostic factors listed below.

Clinical aspects

Patients experiencing reinfection might develop different, similar, or no symptoms at all in comparison with the initial infection. Due to this reason, symptoms were not part of the criteria. An initial way to confirm recovery is that clinical symptoms will disappear (if present), and a negative laboratory RT-PCR test must be obtained to ensure clearance of the virus from the body. Although the presence or absence of symptoms during the initial episode is not necessarily related to the likelihood of reinfection, the conclusions of included studies indicate that a long duration of COVID-19 symptoms and prolonged RT-PCR positivity should not be considered within the context of reinfection as it could be a sign of another condition. Therefore, one month for getting a first negative test was considered in the proposed criteria since the prolonged symptoms of the initial infection, or positivity of the RT-PCR test could last up to a month. Also, for this reason, a minimum of three negative tests in at least three months until a second positive result is proposed, since the majority of other post COVID-19 conditions can last up to 3-months, and in some cases, even longer.

Epidemiological aspect

The developed criteria focused not only on clinical and diagnostic methods, but also gave attention to epidemiological facets such as detection of reinfected cases through an improved surveillance system and public health practices such as contact tracing as methods of broadening and enhancing detection of all cases, whether

symptomatic or asymptomatic. Optimizing follow-up and routine screenings will ensure that reinfected cases are not underestimated, and not only symptomatic cases are detected. This is the first step towards the efficient detection of a confirmed reinfected case using a diversified surveillance system.

In this review, some studies followed the WHO criteria for discharging patients, while others relied on other local discharge criteria to confirm recovery. Due to lack of consistency among studies, as some restricted two negative tests (or more) whereas others required only one, and based on our findings, we proposed at least three negative tests as a unified discharging criteria for confirming viral clearance, preventing false-negative results through multiple testing, and ensuring accuracy of detected reinfected cases. To determine the presence of reinfection, the time between the two infections should be at least 3-months, according to our findings.

Diagnostic aspect

It is well known that RT-PCR is the gold standard molecular diagnostic method for COVID-19 and was used in all included studies as a primary detection method. This diagnostic test, which can be used alone or in conjunction with other diagnostic tests, will allow for a more accurate identification of reinfection. A positive antibody test after seroconversion, as well as detecting a different strain in the second infection via WGS, is confirmatory of a reinfected case. Antibodies to be tested could include IgG, IgM, and IgA. Although viral culture has only been used in a few studies, based on the findings, viral culture will ensure the presence of an active virus.

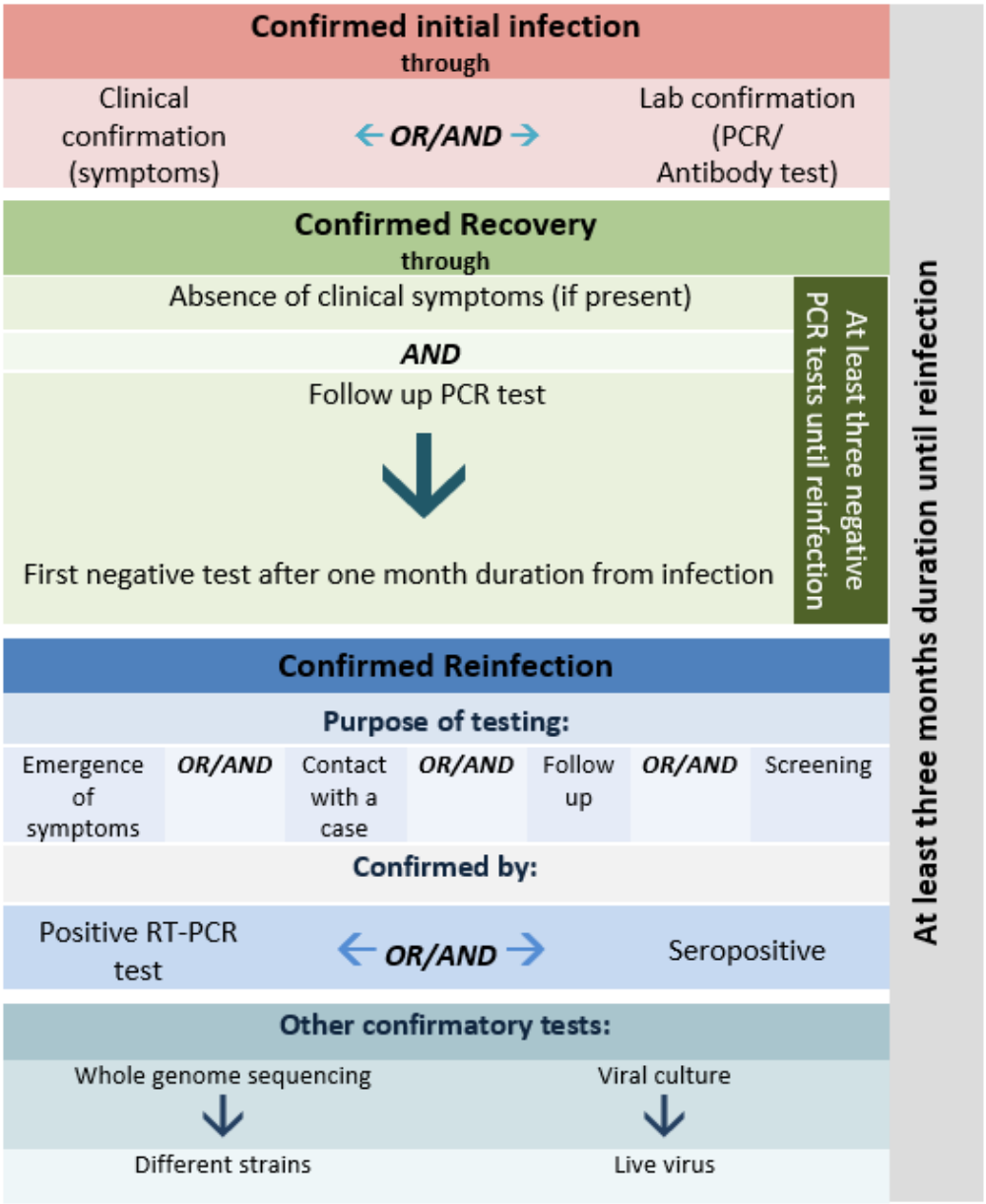

Figure 5. Assessment criteria for SARS-CoV-2 reinfection.

Quality assessment

All included studies were evaluated, and final quality judgments were assigned to each study based on scores (Appendix C). Fourteen case reports and case series were of good quality, while 60 were of fair quality. All studies had a clear objective, clearly defined outcome measures, an adequate length of follow-up, and properly described results as a result of the highly selective inclusion criteria illustrated. The participants in the majority of studies were well defined and described.

For the cohort studies, 17 were fair, and one good. The four cross-sectional studies were all of fair quality. All studies had enough follow-up time for the outcome to occur and did not show the outcome of reinfection at the start of the study. The majority of participants were somewhat representative, had a comparison group drawn from the same community, and provided detailed descriptions of the statistical methods to be used.

Discussion

Reinfection has seldom been reported, and there is no consensus on its definition. Many articles had questionable, non-confirmed outcomes regarding SARS-CoV-2 reinfection, and as such, there is still a gap in understanding how to use the studied terms (re-positivity, relapse, persistence, recurrence, and reactivation) and distinguishing between them and SARS-CoV-2 reinfection**.** This comprehensive scoping review of the literature was carried out to identify variables that were used to define and characterize SARS-CoV-2 reinfection as well as to develop assessment criteria that could be used to distinguish SARS-CoV-2 reinfection from other post COVID-19 conditions that could be confused with.

It has been observed that post COVID-19 conditions may be not distinguished from reinfection in some cases, causing considerable confusion in determining the patient's diagnosis. For instance, many articles and reports published expressed skepticism about the outcome of reported cases, whether they had reinfection or recurrence [230-232], reinfection or reactivation [233-235], reinfection or repositive [236], or reinfection or relapse [237]. Not only are other conditions and reinfection confused, however, conditions are also confused with one another, as one study questioned whether the case had relapse or recurrence [238]. It is also important to note that in some cases, recurrence is used interchangeably with reinfection and relapse [228,

229], while it is also reported independently.

Study findings

Most reinfected cases after at least 6 months from the first infection had an asymptomatic to mild course during reinfection, as one explanation may be due to antibody production in the first infection, leading to protection against aggressive reinfections [239]. Other factors, such as younger age, the absence of comorbidities, and receiving a low dose of the virus when reinfected, could be linked to the emergence of mild cases [240, 241]. Furthermore, when comparing different post COVID-19 conditions for less than 3-months, reinfected cases did not show much of a difference in clinical symptoms. On the other hand, those who were reinfected after 6-months from the initial infection had asymptomatic to moderate symptoms. These disparities could be due to a variety of factors that have yet to be investigated.

Since most reinfected cases occurred after 3-months, this raises concerns about the immune system protection duration, which has implications for global efforts to combat the virus through public health measures as well as immunization programs. A recent unpublished meta-analysis backs up our findings, showing that antibody protection from reinfection lasted at least 6 months [90]. However, for those with factors that may shorten the period of protection, such as immunocompromised people and patients with chronic diseases [242] , a three-month time interval was employed in formulating the assessment criteria.

The majority of cases with persistent SARS-CoV-2 had comorbidities, which was found to be significantly associated with the persistent virus in some studies [243-245]. Recurrence demonstrated a roughly equivalent rate of comorbidity to those with persistent SARS-CoV-2. It was similar to persistence and reactivation in terms of time interval, while it was similar to reinfection and reactivation in terms of symptomatic

status. This could support the claim that COVID-19 recurrence is prompted by SARS-CoV-2 reinfection, SARS-CoV-2 persistence, or SARS-CoV-2 reactivation [121-123]. Relapse is sometimes referred to as reactivation and vice versa [246-248]. However, even though this review observed similarity in terms of time interval until testing positive again, we cannot draw conclusions as only three relapsed cases were included. Among all studied post COVID-19 conditions (except relapse), the main reported reason for testing for the second time was for follow up of patients infected with COVID-19. This demonstrates that in some areas, surveillance measures have been intensively applied to avert any future epidemics.

In terms of immunology, while IgG and IgM were found in a variety of individuals with various post-COVID-19 conditions, IgA was found in just three reinfected cases. IgA is known to be produced two to three weeks after the onset of symptoms in COVID-19 infected cases and to wane by day 28 [249] as it is also involved in the virus's defense mechanism by reducing the infectivity and transmissibility [249]. The primary focus in characterizing immunity has been on IgM and IgG antibodies; however, IgA antibodies, which may contribute to disease pathogenesis, have received far less attention [250], resulting in lower tests for identification of this type.

Outcomes were addressed in this review as reported in included studies, while there is a possibility that these outcomes were not properly identified. This conclusion was based on findings that showed seroconversion being observed in cases of recurrence, reactivation, and persistence in the same way as observed in reinfection.

Five identified cases who underwent WGS were reinfected with the same strain, and as results presented, four of them were reinfected in less than 3-months. This may raise the concern of the possibility of misinterpreting persistent cases as reinfected.

Moreover, 17 cases were reinfected with a different strain in less than three months. The lack of antibody development, waning of antibodies if developed, or occurrence of antibody-dependent enhancement all contribute to the possibility of confirmed reinfection in this short period of time [251-253].

Despite the fact that viral culture is difficult, time-consuming, and requires specialized equipment, it is perhaps the most accurate indicator of having an infection [254]. It was performed in only two studies that included reinfected cases. Because the identified positive result by the PCR test could be due to the presence of dead virus particles, viral culture can be employed to confirm live virus and ensure reinfection in patients.

A key finding of this review is that multiple reinfections or relapses, as seen in some studies, can occur, leading to a chain of infections and multiple positive tests [205, 255]. This fact raises the stakes for further research into the virus' infection chains and potential predictors.

It is noteworthy to mention that some post COVID-19 conditions appeared to be similar in some characteristics to one another. This does not rule out the possibility that these post COVID-19 conditions may be linked, however, conclusions cannot be drawn based on findings of this review. More research on all post COVID-19 conditions separately is needed, as the main focus of this study was to compare these post COVID-19 conditions to reinfection.

Another important point to note is that the word 'mainly' was used in the proposed definitions to describe and distinguish reinfection from other conditions, not to exclude any observed cases that did not fit the definition. Reinfection, for example, does not occur only in middle-aged persons; it may occur in younger or older people as well; however, the vast majority of reinfected cases were middle-aged, thus it was

included in the definition. The same is true for symptom status, as not all reinfected cases exhibit symptoms, and not all of them have the same severity level, for a variety of reasons.

Comparison with other reviews

The majority of studies on SARS-CoV-2 reinfection lack a comprehensive, high-quality methodology needed for including all relevant articles in order to achieve better findings. Even though there have been studies published that propose criteria for defining or diagnosing SARS-CoV-2 reinfection, it is vital to notice the similarities and differences between our findings and those of existing literature.

According to the CDC [256], people infected for a second time in less than 90 days after the first infection must show COVID-19 symptoms or come into contact with a confirmed case to be deemed reinfected. Dissimilar to our findings, which revealed that some instances were reinfected over this time span, were asymptomatic, had no contact with any infected individuals, and had reinfection with a different strain. Yadav et al. [248] defined confirmed reinfection as a second infection occurring more than 90 days after the first infection, with symptoms appearing in the second episode. Our findings, however, revealed variation in symptomatic status and severity, with a noticeable proportion of patients being asymptomatic. As per time interval, one study considered a 102-day time interval between the two infections with a negative test in between as an appropriate definition for reinfected cases [257], while other studies used >90 days [248] and another stated that the longer the time interval, the more likely it is to be reinfection [258].

In one study, six case reports were utilized to define criteria for SARS-CoV-2 reinfection [259], whereas another study reviewed at 13 cases [260]. This could be due to a lack of published studies on the topic at the time the study was conducted, however,

it is well recognized that studies of this nature do not provide solid conclusions; consequently, follow-up studies that investigate this topic in greater depth are to be reviewed in order to obtain reliable estimates. Even though we included a high number of case reports, a fair number of observational studies were also included, in addition to the quality assessment performed, providing strength for our review.

Relapse and recurrence were regarded the same thing in one study [260], while relapse, reactivation, and recurrence were considered the same thing in another study [248] and were further characterized and defined as one thing. According to our findings, there was a noticeable difference in clinical presentations between recurrence and reactivation during the second positive result, as well as changes in seroconversion, implying that recurrence is different that the abovementioned post COVID-19 conditions, but in some instances be triggered by either condition, including reinfection [121-123].

The aforementioned studies differed from our results; nevertheless, it is worth noting that these same studies shared similarities, such as using a time interval of at least 90 days until reinfection and advised whole genome sequencing for reinfection confirmation [248, 256], which is consistent with our findings. Some studies looked into various post COVID-19 conditions in addition to reinfection [248], however, none covered all conceivable post COVID-19 conditions following recovery that could be mistaken or misinterpreted as reinfection.

Strength and limitation of the study

It is imperative to note the strengths and limitations of the present review. In terms of strength, according to our knowledge, this is the first review to assess criteria for defining SARS-CoV-2 reinfection in comparison with all other post COVID-19 conditions identified from the literature, in addition to the comprehensive search and

detailed description of important variables in relation to reinfection. We have transparently reported the methodology used throughout to enable future updates in this area of active publication. Moreover, a fair number of observational studies was included in this review which provides better evidence, in addition to the assessment of quality of all included studies using validated tools.

Several limitations are addressed. First, the articles were clustered in certain WHO regions, with clear gaps in research activities or publications in other areas.

Second, while extensive efforts were incorporated to find a large amount of relevant information to be dissected, it should be acknowledged that the majority of reviewed studies are at the bottom of the hierarchy of evidence (case reports/series) and, thus, have intrinsic limitations for inferences. Therefore, future updates may need to take into account data from study designs rather than case reports/series for demonstrating associations with reinfection.

Third, the number of studies for specific post COVID-19 conditions was relatively low, as only three case reports reported relapse, implying that only three cases were evaluated, rendering it incomparable to other post COVID-19 conditions.

Fourth, many studies had a high risk of false negative tests due to the use of one RT-PCR test to confirm virus clearance from the body after the initial COVID-19 episode, suggesting the possibility of persistence infection rather than true reinfection.

Fifth, an insufficient number of studies performed viral culture and WGS (which provide more robust evidence for confirming the diagnosis of SARS-CoV-2 reinfection), therefore making it difficult to compare among each condition, and therefore were not considered when defining each. Furthermore, only a small percentage of studies documented the Ct value, despite the fact that it is suggested to

do so because it provides additional insight into clinical interpretation [111]. Furthermore, the varying cutoffs specified for the Ct value may impact the evaluation of reinfection when compared to other conditions, therefore were not added to the definitions.

Sixth, the five reinfected cases with a negative viral culture with Ct value more than 30, could indicate that the PCR test discovered dead fragments, implying that the persistent cases might have been misconstrued as reinfection. This could possibly imply that some cases might be misinterpreted as reinfection or vice versa.

Seventh, vaccination is regarded as an essential measure in breaking the transmission chain of SARS-CoV-2 infections, however, it was not reported in the overwhelming majority of studies, as this might be owing to the fact that most national vaccination programs were later implemented.

Eighth, there was a clear lack of reporting of several variables, such as reason for testing, symptomatic status or description of symptoms, and serology data.

Lastly, the number of negative tests may be related to several factors including the patient's occupation (e.g. healthcare workers), patient's condition, as some patients are undergoing therapeutic treatments that may necessitate ongoing routine COVID-19 screening, or usage of a local discharge criteria, which stipulate a minimum number of negative tests required for discharge. This should be accounted for as it provides more confirmatory data for recovery from the initial infection to some groups compared to others. Furthermore, several countries have specific discharge criteria for COVID-19, making three negative tests difficult to implement.

Implications of the study

The findings of this review identified from the literature offer opportunities in

several directions. From the standpoint of future research planning, these findings may allow researchers to further investigate the studied post COVID-19 conditions in further detail. It is of importance to mention the implications of the findings in different contexts. These criteria will help guide healthcare providers in developing a standardized assessment criteria for reinfected patients and in developing early interventions and precision protection programs for the elimination of continuous outbreaks of COVID-19. This study will also help in development of guidelines and implementation of strategies for global public health measures, thereby assisting in impeding the spread of the virus. The findings of this study will aid in the development of guidelines for policies that will assist in combating the disease and minimizing the likelihood of reinfection by implementing appropriate preventative measures, having standardized case definitions to assist in more accurate case investigation, helping in the building of new surveillance systems with the consideration of reinfected patients, and aiding in the development of national immunization programs by accounting for time until reinfection.

Conclusion and recommendations

In conclusion, the issue of SARS-CoV-2 infectivity and re-infectivity continues to be a topic of research. Based on our review of the currently available studies, the role of protection against reinfection remains ambiguous, and subsequent exposure to SARS-CoV-2 and its variants leaves patients vulnerable to a chain of infections. The proposed criteria would aid healthcare professionals in making decisions about public health measures that are to be implemented in countries to reduce the likelihood of reinfection, drive vaccine development and national campaigns, and enhance development of surveillance systems in countries.

An examination of post COVID-19 conditions other than reinfection and the

formulation of assessment criteria for each is important to assist clinicians in making the best diagnosis possible based on high-quality data. When diagnosing patients, it is vital to be cautious, as this can have a lot of clinical and research ramifications. Because there has been such a wide range of reinfected patients, it is crucial to look into the variables that may be driving these disparities, as well as the characteristics of reinfected cases using a uniform case definition. It is also essential to check for reinfection after vaccination, as vaccination rates have risen, and reinfection is projected to decrease. Clinical and laboratory criteria must be utilized to prioritize suspected reinfected cases for additional evaluation due to the restricted availability of regular sequencing capacity [261].

CHAPTER 4: CHARACTERISTICS OF CASES WITH SARS-COV-2 REINFECTION IN QATAR: A CROSS-SECTIONAL STUDY

Background

As COVID-19 pandemic continues to evolve, the likelihood of reinfection among individuals who have recovered is being noticed. There have been several reports of probable reinfections in various parts of the world [58, 97, 262-264]. Although epidemiological and clinical research on SARS-CoV-2 reinfection is increasing, there is still insufficient evidence to draw conclusions about SARS-CoV-2 reinfection. As a result, it is critical to investigate this occurrence and its implications for public health.

Different rates of reinfection were documented based on non-standardized case definitions used, in particular, considering the time period between the two infections. Some researchers utilize time periods longer than or equal to 45 days [265], while others use 90 days or more [266]. Different definitions produce different results. For example, a large study conducted in the United States reported an 11.3% reinfection rate for those reinfected within 30 days, 2.7% for those reinfected 31 to 60 days, 1.1% for those reinfected 61 to 90 days, and 0.3% for those reinfected more than 90 days [87]. This shows a steady decline in rates as the criteria become more stringent, thus it is crucial to compare studies carefully.

Laith Abu-Raddad and colleagues conducted research on SARS-CoV-2 reinfection in Qatar, and they looked into several aspects of the phenomena. For those who had two positive tests after at least 45 days apart, the risk and incidence rates were calculated and found to be 0.04% and 1.09 per 10,000 person-weeks, respectively [265]. The risk ranged between 0.01% and 0.02%, and the incidence rate ranged between 0.38 and 1.06 per 10,000 person-weeks when they included only individuals with a time period of 60 days or longer (sensitivity analysis) [265]. Another study done by the same

author found that patients who were infected once had a 95% probability of not becoming infected again, with protection lasting up to 7 months [267]. This implies that there are disparities in incidence rate and risk of reinfection with COVID-19 with different time interval considered, implying that multiple factors may be involved, emphasizing the significance of further research into such aspects. Among individuals with varying time intervals until reinfection, it requires a better understanding of various characteristics of these patients in order to develop appropriate intervention tactics, provide direction to clinical practice, and increase pandemic-fighting efforts.

During the pandemic, growing rates of asymptomatic and mild COVID-19 infection were observed in situations where individuals use masks. Prior to the widespread use of facial masking, a systematic review of previous studies estimated that 15% of SARS-CoV-2 infections were asymptomatic [268]. A more recent review of 28 studies found an increase in the rate, accounting for 25% asymptomatic of all COVID-19 cases [269]. Recent epidemiologic and virologic evidence has raised the hypothesis that preventive practices may reduce the severity of symptoms of infected people [270]. This prospect is in line with a long-held viral pathogenesis theory that states that the disease severity is proportional to the viral inoculum (the dose of viral particles which triggered infection) received. High doses of viral inoculum can overwhelm and dysregulate innate immune systems in viral infections where host immunity play a vital role in viral pathogenesis, such as SARS-CoV-2, increasing disease severity [271]. The bulk of the research on COVID-19 has focused on the effectiveness of such measures in preventing the spread of viral particles from asymptomatic individuals to others [272, 273], however, less attention has focused on how these practices result in milder disease [270].

Researchers have explored this concept in animal models. For instance, in a Syrian hamster model with SARS-CoV-2 infection, higher virus doses resulted in more severe manifestations, demonstrating the concept of viral inoculum influencing disease manifestations [274]. Additionally, this concept was well studied among humans for several viral pathogens, including influenza virus [275-278], as well as SARS-CoV-2 [240, 279]. According to one report, while all staff in a pediatric dialysis unit in the USA were wearing masks and were exposed to an infected patient, none of the employees who became infected displayed symptoms [280]. Moreover, in outbreaks occurring in US food-processing plants, the asymptomatic rate was 95% among infected patients and always wore masks because since these measures were mandatory [281]. Although asymptomatic infection can be an issue in terms of spreading, case fatality rates have stayed low in nations where masks are required by law, despite the resurgence of cases when lockdowns were lifted [271].

According to the aforementioned findings in the scoping review (Chapter 3 p.26), the symptomatic status of reinfected cases with SARS-CoV-2 were heterogenous with the majority of cases were asymptomatic or having mild symptoms, indicating that there could be possible factors associated with the emergence of symptoms when reinfection occurs. As a result, it is essential to investigate the potential factors that influence the symptoms state of reinfected cases, as this study will be doing, with a particular focus on preventive and risk practices. Furthermore, as per the developed criteria (Chapter 3 p.36), a minimum time gap of 90 days is regarded for reinfected instances otherwise, having less time duration until reinfection (<90 days) could indicate another condition rather than reinfection (e.g. persistence, relapse…etc). For this reason, it is important to explore the characteristics of individuals reinfected after at least 90 days or more (based upon our criteria p.36), as well as study factors related

to the time interval between infections. No studies up to date investigated preventive and risk practices as well as clinical factors associated with symptomatic status of reinfection and how these factors also predict the time interval between the two infections in Qatar.

Aim and objectives

The overarching aim of this study is to describe the sociodemographic, clinical factors, and practices of reinfected cases.

The main objectives are illustrated as the following:

- Objective 1: To quantify the reinfection rate in Qatar between March and June 2021
- Objective 2: To describe the characteristics of reinfected cases by symptomatic status and ordered time interval between the first and second infections
    - To describe the prevalence of symptomatic SARS-CoV-2 reinfected cases
    - To describe the distribution of the time interval between the first and second infections
- Objective 3: To assess the association between preventive and risk practices, and clinical factors with symptomatic status of reinfection and ordered time interval until reinfection

Methods

Study design

This descriptive study utilizes a cross-sectional design using retrospectively collected secondary data from the Ministry of Public Health (MoPH) for case investigation and research purposes. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used to guide the reporting of this study (Appendix D).

Participants and setting

This study included all reinfected cases from March 2021 (start of investigation

of reinfected cases) to June 2021, as the study was conducted in early July 2021 in Qatar. There was no restriction on age or gender for the inclusion of participants as all were eligible if they had a second positive test after at least 90 days or more from the initial test. The total number of infected cases with COVID-19 only once were included to calculate the reinfection rate however were eliminated from further analysis. Figure 6 presents the flowchart of sample derivation.

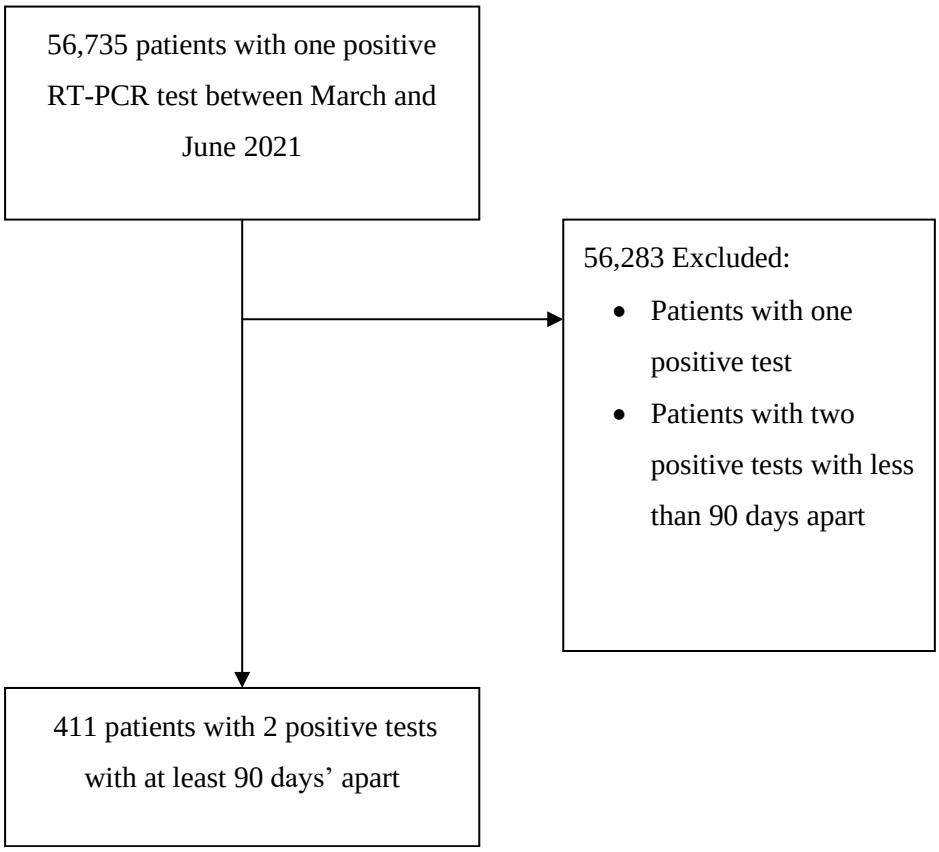

Figure 6. Flow chart of sample derivation.

Data source, data collection, and data management

Data was obtained from the Ministry of Public Health (MoPH), Qatar. The 'Surveillance and Vaccination Electronic System' (SaVES) is a national surveillance system in MoPH, Qatar that receives notifications from all healthcare facilities throughout the country, whether governmental (primarily from Hamad Medical

Corporation (HMC) and Primary Health Care Corporation (PHCC)), semi-governmental, or private. The investigation of cases with a second infection of COVID-19 started on March 2021. Data on sociodemographics and clinical factors were retrospectively collected and further investigation was performed for preventive and risk practices after the first infection upon request for the aim of conducting this study. These preventive practices were wearing masks, hand hygiene, and social distancing, while the risk practices investigated included physical contact with other and attending social gatherings. The investigation of preventive and risk practices was conducted by phone calls, with each patient being asked if they had continued to implement these practices after the first infection. Based on the answer of the patient, the trained case investigator added the answer to one of the following categories as appropriate: never, sometimes, or always. These examined variables were determined by the MoPH to be the most widespread practices in the country and based on vital as individual public health measures reported in the literature found effective in protection during the COVID-19 pandemic. The anonymous data was appropriately cleaned and prepared for data analysis. To evaluate the validity of each variable, the range of values was examined, and missing values were checked.

Measures

Table 6 presented the summary of measures.

Outcome variables

- Existence of Symptomatic status during the second infection, measured exclusively as the presence of any COVID-19 symptoms (Yes, No).
- Time interval between the first and second infections in days, calculated as the time between the date of the first positive test and the date of the second positive test. For analysis, the duration was further categorized through quantile cutoffs.

For reinfected cases in at least 90 days, it was classified into ("≤275=less time", "276-309=medium time", "310-333=long time", and "≥334=longest time"). Since the case investigation of those with a second infection was based upon time interval from Abu-Raddad's et al. study [265], other factors such as the number of and duration until negative tests—as confirmed recovery—were not considered in the criteria when investigating reinfected cases.

Main independent variables: preventive and risk practices after the first infection

Preventive practices after the first infection performed on an individual level were wearing masks, observing hand hygiene, and maintaining social distancing, as were measured using the following responses: ("Never", "Sometimes", and "Always").

Risk practices after the first infection were defined as social gathering and physical contact, which were also measured by the latter categorization.

For analysis, two new variables were created, namely, preventative practices and risk practices, which were operationalized from the parameters indicated above. Each individual variable was given a score: never=0, sometimes=1, and always=2, and were summed up. The maximum score was six for combined preventive practices which indicated always performing all practices (wearing masks, observing hand hygiene, and maintaining social distancing), while other less scores indicated sometimes performing some of these practices. A score of zero was not present for combined preventive practices. Therefore, were grouped into categories ("Sometimes" and "Always"). For the combined risk practices, the minimum score number was zero indicating never performing any of these practices (physical contact and attending social gatherings), while other higher scores implied sometimes or always engaging in some or all of these risk practices. They were further grouped as ("Never" and "Sometimes or always").

Other variables

Sociodemographic variables

Age was classified as ("≤20", "21-40", "41-60", and "≥61") for description, and was further categorized as ("≤35" and ”>35") for data analysis since findings of a study examining factors affecting symptomatic status found a significant association between older age “>35" and symptomatic status of COVID-19 [282]. Gender was reported as "male" and "female". Nationality was categorized as ("Arabs", "Asians", "Other") and was further narrowed as ("Arabs" and "Non-Arabs") for analysis purposes. Based on the MoPH classification, occupations were classified as ("Blue collar workers," "White collar workers," "Healthcare workers," "Administrative", "Army and police", "Unemployed, retired, housewives", and "Students and children"). For this study, "Admin" and "Army and police" were combined and classified as "Other Workers", while "Unemployed, retired, housewives" and "Students and children" were considered as "Not working".

Clinical variables

Symptomatic status for the first infection was reported as either "Yes" or "No". Hospitalized patients, which may indicate the severity of a case, were reported as ("Yes" or "No"). Vaccination status before reinfection was generated from the dates of the first/second dose (if taken after the first infection) and date of reinfection and was categorized as ("Yes, fully vaccinated," "Yes, one dose," and "Not vaccinated"). For those who took any dose of the vaccine were put in one group, which is ("At least one dose") for analysis. Duration from vaccination until reinfection was calculated in days based on dates from first/second dose to reinfection. The duration from the first positive to the first negative was also calculated for descriptive purposes.

Table 6. Summary of Outcome and Independent Variables

Variable	Measures
Outcome variables:	
Symptom's status of reinfection	Categorized (Yes/No)
Time interval between the first and second infections	In days Categorized (less time, medium time, long time, longest time)
Independent variables:	
Age	In years Categorized (≤35, >35)
Gender	Categorized (Male, Female)
Ethnicity	Categorized (Arab, Non-Arab)
Occupation	Categorized (Blue collar workers, White collar workers, Healthcare workers, Other workers, Not working)
Symptomatic status of first infection	Categorized (Yes, No)
Hospitalization status of first infection	Categorized (Yes, No)
Vaccination status before reinfection	Categorized (Yes at least one dose, Not vaccinated)
Combined preventive practices*	Categorized (Sometimes, Always)
Combined risk practices**	Categorized (Always or sometimes, Never)

Note: * Performing all preventive practices including wearing mask, keeping social distance, and hand hygiene after the first infection

** Performing all risk practices including physical contact and attending social gathering

Definitions

Reinfection with time interval of at least 90 days was defined in accordance with findings of the scoping review (Chapter 3 p.36). Variables included in this study are all defined in Table 7.

Table 7. Definitions of Variables

Variable	Definition
Reinfection	Those who tested positive for PCR 90 days or more after an initial positive test as per findings of scoping review (Chapter 3 p. 36)
Wearing Mask after first Infection	Wearing any type of mask
Keeping social distance after first Infection	Keeping a gap of one meter between people
Hand hygiene after first infection	Hand washing with soap or rubbing with a hand sanitizer
Combined preventive practices after the first infection	Performing all preventive practices (wearing masks, keeping social distancing, and hand hygiene)
Physical contact after first Infection	Any direct physical contact (handshaking, hugging...etc)

Social gathering after first Infection	Attending occasions and family visits
Combined preventive practices after the first infection	Engaging in all risk practices (physical contact and attending social gatherings)
Symptomatic status	Cases with exclusively any COVID-19 symptoms were considered to be symptomatic
Asymptomatic status	With no COVID-19 symptoms
Hospitalization status	Admitted to either the acute care unit or the intensive care unit (ICU)

Statistical analysis

Descriptive statistics were used to summarize characteristics of reinfected patients through frequencies and percentages if variables were categorized, while mean and standard deviation or median and interquartile range were used if variables were continuous depending on the distribution of the variable.

Univariate and multivariable logistic regression were used to study association between variables of symptomatic status of reinfection and time interval between the first and second infections. Using logistic regression and ordinal logistic regression for the latter outcomes, respectively, three sets of models were generated for each outcome to study how the effect estimates altered with different variables included in the model. Model 1 included preventive and risk practices variables with confounders adjustment; Model 2 included clinical variables such as symptomatic status of first infection, hospitalization status of first infection, and vaccination status before reinfection with confounders adjustment; and Model 3 included all clinical and practice variables with confounders adjustment. Furthermore, comparison between nested models was conducted using likelihood ratio tests (with p-value <0.05 considered significant) to discover the most parsimonious model and to assess whether the additional explanatory variables improved the model fit. Complete case analysis was performed as missing data in each variable, as well as fitting the models, did not exceed 3%.

Confounders selected for adjustment in the models were considered using a

Directed Acyclic Graph (DAG) that was created using a browser-based software DAGitty [283]. DAGs are a graphical tool for visually representing and better understanding causal relationships, identifying confounding factors, and reducing the potential bias in the estimate [284, 285]. Factors considered in the DAG included age, sex, nationality, occupation, symptoms of the first infection, symptoms of the second infection, hospitalization status of the first infection, hospitalization status of the second infection, combined preventive practices and combined risk practices, time interval between the first and second infections, and vaccination before reinfection. Two DAGs were constructed for each outcome (Appendix E), and confounders identified by the DAG were integrated into the multivariable models. For the time interval outcome, identified confounders were, age, sex, and nationality. The same confounders were identified for the symptomatic status of reinfection outcome in addition to occupation.

After running the regression analyses, multi-collinearity among the independent variables was examined for by using the variance inflation factors (VIF). None of the variables reached a value of 5, indicating the potential for multi-collinearity between the independent variables [286]; therefore, it was not necessary to remove any of the variables from the analysis. The proportional odds assumption was further tested for the ordinal logistic regression using the brant test and the generalized ordinal model using STATA [287], with no violations observed in the final model.

STATA version 17.0 [288] was used for analysis and two-sided p-value <0.05 was considered statistically significant. Brant and gologit2 commands were used for testing the proportional odds assumption in STATA [287]. The results of regression analyses were presented as prevalence odds ratios (POR), odds ratios (OR), 95% confidence intervals (95% CI), and p-values. The POR was employed using an unconditional logistic regression since we had prevalent cases with symptomatic status

of reinfection.

Ethical approval

An exemption was obtained from the MoPH-IRB and QU-IRB with references of ERC-826-3-2020 and QU-IRB 1601-E/21 respectively since this study did not involve human subjects. The study was conducted on de-identified data which was saved in a password-protected laptops.

Results

Reinfection rate in Qatar

Out of 56,735 who had a confirmed PCR positive test between March and June 2021, a total number of 411 participants equal to a rate of 0.73% (95% CI= 0.66%, 0.80%) were reinfected cases with time interval ≥90 days.

Characteristics of reinfected cases

Among the 411 reinfected cases after at least 90 days, the mean age was 33.88 (SD: 10.73) years, among them, the highest age group falling between ages of 21 and 40 years (Appendix G: Table A 7). The overwhelming majority of included participants were males accounting for 84%. Most were of Asian origin, followed by an Arab origin, accounting for 76% and 22%, respectively. The greater part of reinfected cases were blue collar workers (57%), followed by 16% of white-collar workers. Few proportion of patients with reinfection were healthcare workers (5%) (Appendix G: Table A 7).

More than half had symptoms during the first infection, while less than half had symptoms during the second. However, 54% had similar clinical presentation in both infections and 31% worsened from asymptomatic in the first infection to symptomatic disease during reinfection. Furthermore, only 14% of those who were hospitalized in the first infection were hospitalized in the second, and 7.5% of those who were symptomatic during reinfection were hospitalized, indicating severity of reinfection.

Few people were vaccinated before being reinfected, with only 3.6% receiving the first dose and 3.6% being fully vaccinated.

After the first infection, the majority of people continued to practice individual prevention measures, with 91% wearing masks, 83% maintaining social distance, and 86% keeping their hands clean. Risk practices were also neglected after the first infection, with 73% never having physical contact and 71% never attending social gatherings. Despite this, it is important to note that some of the participants failed to follow preventive practices and engaged in risk practices. The most common reasons for testing in the first infection was contact with a case and clinical suspicion, while the most common reasons for testing in the second infection were clinical suspicion and routine surveillance. Seventy two percent of those with time interval <90 days had no negative tests in between, followed by 12% with one negative test, 8% with two, and 8% with three or more.

Only 2 cases in this study met the criteria developed in the scoping review to be considered as reinfection which comprises of having at least 3 negative tests between the first and second infections with one month until the first negative tests and time interval not less than 90 days from the first infection until reinfection.

Symptomatic status of reinfection

Characteristics of reinfected cases by symptomatic status

The prevalence of symptomatic patients was equal to 39% (CI 95%: 34.6%,44.1%) in those reinfected in at least 90 days (Table 8). While the age distribution of symptomatic and asymptomatic cases was nearly identical, the number of males (90%), Asian nationality (83%), always wearing masks (94%), always maintaining social distance (89%), always maintaining hand hygiene (90%), never being in physical contact (82%), and never attending social gatherings (77%) were all higher among those

with asymptomatic disease during reinfection. Additionally, those who consistently practice all of the above-mentioned preventive measures (85%), as well as those who never engage in any of the above-mentioned risk practices (70%), are also found to be asymptomatic. Moreover, those who had symptoms during reinfection had slightly shorter median days until reinfection (306, IQR= 275-330) compared to the median days of asymptomatic reinfected cases (311, IQR= 275-336). Table 8 summarizes characteristics of reinfection case after at least 90 days by symptomatic status of reinfection.

Table 8. Characteristics of Reinfected Cases After at Least 90 Days by Symptomatic Status of Reinfection

	Symptomatic status of reinfection	
	Yes	No
	N=161	N=249
Age in years*	34.73±11.29	33.36±10.35
Age categorized		
≤20	9 (5.6%)	17 (6.8%)
21-40	116 (72.0%)	177 (71.1%)
41-60	32 (19.9%)	54 (21.7%)
>60	4 (2.5%)	1 (0.4%)
Gender		
Female	40 (24.8%)	24 (9.6%)
Male	121 (75.2%)	225 (90.4%)
Nationality		
Other	6 (3.7%)	5 (2.0%)
Arab	51 (31.7%)	38 (15.3%)
Asian	104 (64.6%)	206 (82.7%)
Occupation		
Blue Collar Workers	73 (45.3%)	163 (65.5%)
White Collar Workers	36 (22.4%)	30 (12.0%)
Healthcare Workers	12 (7.5%)	7 (2.8%)
Admin	12 (7.5%)	11 (4.4%)
Army and police	8 (5.0%)	13 (5.2%)
Students and children	9 (5.6%)	11 (4.4%)
Unemployed, Retired and Housewives	11 (6.8%)	14 (5.6%)
Symptomatic status of first Infection		
No	52 (32.3%)	113 (45.4%)
Yes	108 (67.1%)	134 (53.8%)
Missing	1 (0.6%)	2 (0.8%)
Hospitalization status of first Infection		
No	139 (86.3%)	229 (92.0%)

	Symptomatic status of reinfection	
	Yes	No
	N=161	N=249
Yes	21 (13.0%)	16 (6.4%)
Missing	1 (0.6%)	4 (1.6%)
Hospitalization status of reinfection		
No	148 (91.9%)	243 (97.6%)
Yes	12 (7.5%)	0 (0.0%)
Missing	1 (0.6%)	6 (2.4%)
Vaccination status before reinfection		
No	146 (90.7%)	234 (94.0%)
Yes, fully vaccinated	7 (4.3%)	8 (3.2%)
Yes, first dose	8 (5.0%)	7 (2.8%)
Days between vaccination and reinfection after full dose** (n=14) §	27 (13-55)	17 (4-31)
Days between vaccination and reinfection after one dose** (n=14) §	6.5 (3-15.5)	6.5 (4.5-10.5)
Time interval between the first and second infections in days**	306 (275-330)	311 (275-336)
Reason for testing first infection		
Clinical suspicion	71 (44.1%)	53 (21.3%)
Contact of a case	61 (37.9%)	87 (34.9%)
Routine surveillance	25 (15.5%)	77 (30.9%)
Port of entry	3 (1.9%)	30 (12.0%)
Missing	1 (0.6%)	2 (0.8%)
Reason for testing reinfection		
Clinical suspicion	82 (50.9%)	70 (28.1%)
Contact of a case	18 (11.2%)	17 (6.8%)
Routine surveillance	37 (23.0%)	92 (36.9%)
Port of entry	24 (14.9%)	70 (28.1%)
Wearing Mask after first infection		
Never	2 (1.2%)	1 (0.4%)
Sometimes	17 (10.6%)	12 (4.8%)
Always	141 (87.6%)	233 (93.6%)
Missing	1 (0.6%)	3 (1.2%)
Keeping social distance after first infection		
Never	8 (5.0%)	3 (1.2%)
Sometimes	34 (21.1%)	21 (8.4%)
Always	118 (73.3%)	222 (89.2%)
Missing	1 (0.6%)	3 (1.2%)
Hand hygiene after first infection		
Never	3 (1.9%)	1 (0.4%)
Sometimes	28 (17.4%)	22 (8.8%)
Always	129 (80.1%)	223 (89.6%)
Missing	1 (0.6%)	3 (1.2%)
Physical contact after first infection		
Never	96 (59.6%)	204 (81.9%)
Sometimes	45 (28.0%)	30 (12.0%)
Always	18 (11.2%)	12 (4.8%)
Missing	2 (1.2%)	3 (1.2%)
Social Gathering after first infection		

	Symptomatic status of reinfection	
	Yes	No
	N=161	N=249
Never	102 (63.4%)	191 (76.7%)
Sometimes	52 (32.3%)	49 (19.7%)
Always	6 (3.7%)	6 (2.4%)
Missing	1 (0.6%)	3 (1.2%)
Combined preventive practices		
Sometimes[+]	57 (35.4%)	35 (14.1%)
Always[++]	103 (64.0%)	211 (84.7%)
Missing	1 (0.6%)	3 (1.2%)
Combined risk practices		
Never[+++]	73 (45.3%)	174 (69.9%)
Sometimes or always[++++]	86 (53.4%)	72 (28.9%)
Missing	2 (1.2%)	3 (1.2%)

Note: Data are presented as n (%) for categorical measures.

[*] Presented as mean ±SD [**] Presented as Median (IQR)

[+]Sometimes perform some of the preventive practices [++]Always perform all preventive practices

[+++]Never engage in any risk practice [++++]Sometimes engage in some risk practices or always engage in all risk practices

[§] One case with missing data

Factors associated with symptomatic status of reinfection in reinfected cases

This analysis studies association between the combined preventive and risk practices with symptomatic status of reinfection. It is also comprised of three models. The goodness of fit tests revealed that Model 1 for preventive practices and risk practice variables, and Model 3 for clinical variables showed a better fit of data as the p-value of likelihood ratio test was equal to 0.181 and <0.001, respectively.

Table 9 shows the univariate and multivariable analysis with the combined preventive measures. It is worth noting that in the univariate analysis, combined preventive measures were found to be positively associated with symptomatic status of reinfection; however, when adjusted for confounders in Models 1, this association flipped. It is interpreted as the prevalence odds of developing symptoms in reinfection was 59% (95% CI= 0.24,0.72, P= 0.002) lower among those who always practice all

combined preventive measures (wearing masks, social distancing, and hand hygiene) compared to those who sometimes perform some of these practices.

Performing combined risk practices was also found to be strongly and significantly associated with symptomatic status of reinfection before and after accounting for confounders. For instance, those who sometimes or always performed some or all of risk practices (physical contact and social gatherings) had significantly higher prevalence odds of developing symptomats during reinfection compared to those who were never engaged in such practices (aPOR= 1.94, 95% CI= 1.21,3.12, P= 0.006).

As per clinical factors, the symptomatic status of the first infection had increased odds of developing symptoms during reinfection (aPOR= 1.65, 95% CI= 1.03,2.63, P= 0.035). An insignificant weak association between hospitalization status of the first infection (aPOR= 1.04, 95% CI= 0.47,2.29, P= 0.926) and vaccination status (aPOR= 1.06, 95% CI= 0.45,2.49, P= 0.895) with the outcome was also observed.

Age was not found to be associated with symptomatic status of reinfection. Male gender is strongly and statistically significantly associated with symptomatic phase of a disease making them less likely to develop symptoms during reinfection compared to females. Arab nationality showed strong association with developing symptoms during reinfection compared to non-arabs. All workers in different sectors seemed to have a higher prevalence odd of symptomatic course compared to non-workers, showing significance only in the white-collar workers group. It is important to mention that healthcare workers had the highest the prevalence odds of symptomatic status of reinfection when compared to cases not working.

Table 9. Univariate and Multivariable Logistic Regression Analysis for Symptomatic Status of Reinfection with Combined Prevetive and Risk Practices for Reinfected Cases After at Least 90 Days

	Univariate analysis		Multivariable analysis					
			Model 1		Model 2		Model 3	
	POR [95% CI]	p-value	aPOR [95% CI]	p-value	aPOR [95% CI]	p-value	aPOR [95% CI]	p-value
Age								
≤35	Reference							
>35	1.01 [0.67,1.51]	0.966	1.01 [0.65,1.57]	0.955	1.05 [0.68,1.63]	0.825	0.99 [0.63,1.56]	0.975
Gender								
Female	Reference							
Male	0.32 [0.18,0.56]	**<0.001**	0.40 [0.19,0.85]	**0.017**	0.46 [0.22,0.96]	**0.039**	0.42 [0.20,0.89]	**0.023**
Nationality								
Non-Arab	Reference							
Arab	2.57 [1.59,4.16]	**<0.001**	1.54 [0.74,3.19]	0.247	2.23 [1.10,4.55]	**0.027**	1.54 [0.73,3.25]	0.258
Occupation								
Not working	Reference							
Healthcare Workers	2.14 [0.71,6.45]	0.175	2.41 [0.69,8.48]	0.169	2.79 [0.82,9.48]	0.099	2.17 [0.61,7.69]	0.230
White Collar Workers	1.50 [0.70,3.21]	0.297	3.85 [1.40,10.54]	**0.009**	3.46 [1.30,9.22]	**0.013**	3.95 [1.42,10.98]	**0.009**
Other workers	1.04 [0.45,2.40]	0.924	1.88 [0.68,5.15]	0.221	1.76 [0.65,4.78]	0.270	1.84 [0.65,5.25]	0.253
Blue Collar Workers	0.56 [0.29,1.07]	0.080	1.75 [0.64,4.77]	0.274	1.68 [0.63,4.45]	0.300	1.76 [0.64,4.86]	0.273
Combined preventive practices								
Sometimes	Reference							
Always	3.19 [2.01,5.05]	**<0.001**	0.41 [0.24,0.72]	**0.002**	-		0.42 [0.24,0.74]	**0.003**
Combined risk practices								
Never	Reference							
Sometimes or always	1.97 [1.27,3.07]	**0.002**	1.94 [1.21,3.12]	**0.006**	-		2.07 [1.27,3.36]	**0.003**
Symptom’s status of the first infection								
No	Reference							
Yes	1.75 [1.16,2.65]	**0.008**	-		1.55 [0.99,2.41]	0.051	1.65 [1.03,2.63]	**0.035**

	Univariate analysis		Multivariable analysis					
			Model 1		Model 2		Model 3	
	POR [95% CI]	p-value	aPOR [95% CI]	p-value	aPOR [95% CI]	p-value	aPOR [95% CI]	p-value
Hospitalization status of first infection								
No	Reference							
Yes	2.16 [1.09,4.28]	**0.027**	-		1.47 [0.69,3.13]	0.322	1.04 [0.47,2.29]	0.926
Vaccination before reinfection								
No	Reference							
At least one dose	1.60 [0.76,3.37]	0.215	-		0.97 [0.42,2.23]	0.936	1.06 [0.45,2.49]	0.895

Time interval between the first and second infections

Characteristics of reinfected cases by ordered time interval

Time interval between the first and second infections was categorized into four ordered groups (less time, medium time, long time, and longest time) according to quantiles.

Table 10 demonstrates characteristics of reinfected patients by ordered time interval. The mean age of all the four groups of ordered time intervals was nearly identical, while age categories with less time included more younger participants aged less than or equal to 20 years. Males predominated in all groups accounting between 86% to 97%, with the exception of those with less time intervals, which had a higher proportion of females (33%). Asians were having long time intervals compared to Arabs and other nationalities. Blue collar workers had higher time intervals until reinfection, while unemployed, housewives and retired, in addition to students and children had had less time interval until reinfection.

Majority of cases with symptomatic status in the first infection had less time interval until reinfection (67.3%) compared to those with no symptoms. However, hospitalization status of the first infection was clustering among less (9.6%), medium (9.7%), and long (9.8%) time interval, with a smaller number of them having longest time interval until reinfection (6.9%).

Despite having similar time distribution among individual preventive practices, those who always wore masks (94.1%), kept social distance (92.2%), or performed hygiene their hands (92.2%) had longest time interval until reinfection compared to those who sometimes or never perform these individual practices. Moreover, cases who never engage in physical contact (81.4%) or attend social gatherings (75.5%) also had longest time intervals until reinfection. What's more, cases with longest time interval

had a high proportion of patients with at least one negative tests between the first and second infections when compared to other groups. Cases with longest time interval also had a higher proportion of people who always perform all combined preventive practices (86.3%) compared to those who sometimes performed some of these practices which had less time interval until reinfection. Similarly, those who never engage in any risk practice had longest time interval (68.6%).

Table 10. Characteristics of Reinfected Cases After at Least 90 days by Ordered Time Interval

	Less time N=104	Medium time N=103	Long time N=102	Longest time N=102
Age in years*	32.60±11.70	33.91±11.56	35.79±9.82	33.23±9.50
Age categorized				
≤20	13 (12.5%)	9 (8.7%)	1 (1.0%)	3 (2.9%)
21-40	77 (74.0%)	64 (62.1%)	77 (75.5%)	76 (74.5%)
41-60	11 (10.6%)	30 (29.1%)	22 (21.6%)	23 (22.5%)
>60	3 (2.9%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
Gender				
Female	34 (32.7%)	14 (13.6%)	3 (2.9%)	13 (12.7%)
Male	70 (67.3%)	89 (86.4%)	99 (97.1%)	89 (87.3%)
Nationality				
Other	3 (2.9%)	2 (1.9%)	3 (2.9%)	3 (2.9%)
Arab	36 (34.6%)	24 (23.3%)	12 (11.8%)	17 (16.7%)
Asian	65 (62.5%)	77 (74.8%)	87 (85.3%)	82 (80.4%)
Occupation				
Blue Collar Workers	41 (39.4%)	63 (61.2%)	63 (61.8%)	69 (67.6%)
White Collar Workers	14 (13.5%)	16 (15.5%)	23 (22.5%)	13 (12.7%)
Healthcare Workers	13 (12.5%)	2 (1.9%)	2 (2.0%)	2 (2.0%)
Admin	9 (8.7%)	8 (7.8%)	4 (3.9%)	2 (2.0%)
Army and police	8 (7.7%)	3 (2.9%)	5 (4.9%)	5 (4.9%)
Students and children	8 (7.7%)	8 (7.8%)	1 (1.0%)	3 (2.9%)
Unemployed, Retired and Housewives	11 (10.6%)	3 (2.9%)	4 (3.9%)	8 (7.8%)
Symptomatic status of first Infection				
No	34 (32.7%)	45 (43.7%)	39 (38.2%)	47 (46.1%)
Yes	70 (67.3%)	58 (56.3%)	61 (59.8%)	53 (52.0%)
Missing	0 (0.0%)	0 (0.0%)	2 (2.0%)	2 (2.0%)
Hospitalization status of first Infection				
No	92 (88.5%)	93 (90.3%)	90 (88.2%)	93 (91.2%)
Yes	10 (9.6%)	10 (9.7%)	10 (9.8%)	7 (6.9%)

	Less time N=104	Medium time N=103	Long time N=102	Longest time N=102
Missing	2 (1.9%)	0 (0.0%)	2 (2.0%)	2 (2.0%)
Vaccination status before reinfection				
No	93 (89.4%)	99 (96.1%)	93 (91.2%)	96 (94.1%)
Yes, fully vaccinated	7 (6.7%)	2 (1.9%)	5 (4.9%)	1 (1.0%)
Yes, first dose	4 (3.8%)	2 (1.9%)	4 (3.9%)	5 (4.9%)
Combined preventive practices				
Sometimes[+]	30 (28.8%)	29 (28.2%)	21 (20.6%)	12 (11.8%)
Always[++]	73 (70.2%)	74 (71.8%)	79 (77.5%)	88 (86.3%)
Missing	1 (1.0%)	0 (0.0%)	2 (2.0%)	2 (2.0%)
Combined risk practices				
Never[+++]	56 (53.8%)	57 (55.3%)	64 (62.7%)	70 (68.6%)
Sometimes or always[++++]	47 (45.2%)	46 (44.7%)	35 (34.3%)	30 (29.4%)
Missing	1 (1.0%)	0 (0.0%)	3 (2.9%)	2 (2.0%)

Note: Data are presented as n (%) for categorical measures.

[*] Presented as mean ±SD [**] Presented as Median (IQR)

[+]Sometimes perform some of the preventive practices [++]Always perform all preventive practices [+++]Never engage in any risk practice [++++]Sometimes engage in some risk practices or always engage in all risk practices

Factors associated with ordered time interval between the first and second infections

This analysis investigate association between combined preventive and risk practices with ordered time interval until reinfection. Models 1 and Model 3 were better fitting the data for practice variables and for clinical variables, respectively.

Table 11 illustrates the univariate and multivariable analysis for the combined preventive and risk practices. The regression analyses discovered that the odds of those with longest time interval versus combined other durations was 57% (95% CI= 95% CI= 1.00,2.48, P= 0.051) higher among cases who always performed all combined preventive practices compared to who sometimes practiced some of these preventive measures. Risk practices did not show significant association with time interval after accounting for confounding, but still presented an association with shorter time durations until reinfection (aOR= 0.81, 95% CI= 0.55,1.20, P= 0.291).

The odds of those with longest time interval vs. combined other durations was 27% (95% CI= 0.51,1.06, P= 0.104) lower in cases with symptoms in the first infection compared to asymptomatic cases. For hospitalization status of the first infection, it had higher odds of longest time durations by 40% (95% CI= 0.73,2.68, P= 0.313) when compared to non-hospitalized patients in the first infection. Vaccination status had a weak association with time interval until reinfection (aOR= 0.92, 95% CI= 0.44,1.90, P= 0.822).

Age did not seem to have a valuable association with time interval. Male gender showed strong positive and significant association with higher odds with longest time interval versus the combined shorter intervals. It is noteworthy that Arabs were also found to have lower odds of longest time interval compared to non-arabs.

Table 11. Univariate and Multivariable Ordinal Logistic Regression Analysis for Time Interval Between the First and Second Infections with Combined Prevetive and Risk Practices for Reinfected Cases After at Least 90 Days

	Univariate analysis		Multivariable analysis					
			Model 1		Model 2		Model 3	
	OR [95% CI]	p-value	aOR [95% CI]	p-value	aOR [95% CI]	p-value	aOR [95% CI]	p-value
Age								
≤35	Reference							
>35	1.06 [0.75,1.51]	0.723	1.05 [0.73,1.50]	0.784	0.98 [0.68,1.42]	0.940	1.01 [0.70,1.47]	0.934
Gender								
Female	Reference							
Male	3.59 [2.12,6.09]	**<0.001**	2.92 [1.63,5.23]	**<0.001**	2.90 [1.62,5.19]	**<0.001**	3.00 [1.66,5.40]	**<0.001**
Nationality								
Non-Arab	Reference							
Arab	0.44 [0.28,0.68]	**<0.001**	0.75 [0.46,1.25]	0.274	0.65 [0.39,1.07]	0.091	0.78 [0.46,1.31]	0.347
Combined preventive practices								
Sometimes	Reference							
Always	1.92 [1.27,2.91]	**0.002**	1.57 [1.00,2.48]	0.051	-		1.53 [0.97,2.44]	0. 067
Combined risk practices								
Never	Reference							
Sometimes or always	0.62 [0.43,0.89]	**0.010**	0.81 [0.55,1.20]	0.291	-		0.76 [0.51,1.15]	0.195
Symptom's status of the first infection								
No	Reference							
Yes	0.73 [0.51,1.03]	0.078	-		0.75 [0.52,1.08]	0.123	0.73 [0.51,1.06]	0.104
Hospitalization status of first infection								
No	Reference							
Yes	0.83 [0.45,1.50]	0.536	-		1.19 [0.63,2.26]	0.587	1.40 [0.73,2.68]	0.313
Vaccination before reinfection								
No	Reference							
At least one dose	0.75 [0.38,1.49]	0.409	-		0.99 [0.48,2.04]	0.984	0.92 [0.44,1.90]	0.822

Discussion

Understanding the features of reinfected cases is becoming increasingly important as global reinfection rates rise. The factors that determine the symptomatic status of reinfection and the time gap till reinfection are investigated in this study.

Reinfection rate and characteristics of reinfected cases

The overall reinfection rate was equal to 0.73% between March and June 2021 for cases who got the second infection after at least 90 days from the first infection. Other findings with similar case definition showed lower rates which equaled 0.17% in Czech Republic [98], while another study conducted in which additionally required at least one negative test between the first and second infections as confirmatory for reinfection accounted for 0.47% [106]. A study conducted in Italy with at least 2 negative tests required as part of discharge criteria had a reinfection rate of 0.33% [289]. Large cohort studies considering the mentioned time interval in England [88], Italy [290], and Switzerland [100] also showed rare occurrence of reinfection not exceeding 1%. This variation in rates could be due to several reasons including ununified case definition for reinfected cases, demographic or geographical factors, vaccination status, type and rate of immune response, and policies and preventive measures imposed in the country in regards to COVID-19 [291]. According to a prior study conducted in Qatar by Laith Abu-Raddad and colleagues, the rate of reinfection for those reinfected after at least 45 days was 0.18% [265]. This increase in the rate in Qatar could be due to multiple reasons including, different methods and study designs employed, different time duration of included participants, and also due to the increase in number of COVID-19 cases during the period of the study.

The mean age was 34 of cases reinfected after at least 90 days, as it was not quite similar to ages of other reinfected cases with similar case definition which were 50 years in France [106], and 54 years in Italy [289]. This discrepancy could be due to

the special demographic structure in Qatar which mainly comprises of adult males aged 20 to 50 years, with a high proportion of labor workers [292]. Another factor could be the widespread reimplementation of COVID-19 protection measures in Qatar in 26th of March, 2021 after the spread of the UK variant, including regulations for children under 12 years old, such as school disclosures and restricting them from attending particular locations [293]. Despite the fact that just a few elderly people were included in our study, they were given priority for the first baches of vaccine in the country, which could have shielded them from future reinfections [294]. Special attention was given to these two groups (children and elderly) as further guidelines were published by the Ministry of Public Health for the public regarding precautionary measures to be undertaken to protect them from getting infected with COVID-19 [295].

SARS-CoV-2 reinfection seemed to have a stronger association with males which accounted for 84% in this study, while in other studies described lower rates which were equal to 54% in France [106], 37.5% in Italy [289], and 19% in England [88]. This could be due to a variety of factors, including the fact that Qatar has a higher proportion of males (75%) than females [296]. The vast majority of individuals reinfected in this study were Asians and blue-collar employees, as manual workers accounting for roughly 60% of the entire population in Qatar and being predominantly adult males with mostly being of Asian and African nationalities [297]. Due to labors work requirements, they are more likely to work in densely populated regions than females. Working in these environments may increase the likelihood of getting reinfected. Moreover, some studies presented males may have poorer adherence to preventative measures than females, making them more susceptible to reinfection [298, 299]. Furthermore, different immune reactions between males and females may arise due to hormonal systems in females, particularly the dominant female hormone

estrogen, which may confer protection from infection with COVID-19 [300]. Consequently, males have more severe course of COVID-19 disease requiring intensive care unit admission [301], our findings showed that males accounted for 92% of those hospitalized in the second infection and 75% males had symptoms during reinfection when compared to females.

Hospitalization status of the second infection was equal to 3.4% among reinfected cases, which was substantially lower than another study in Italy, which reported that 17% of reinfected patients were hospitalized [289]. This could indicate that reinfected cases in Qatar are generally less severe, either as a result of efficient COVID-19 case treatment or due to variances in body defense among various populations [302]. The percentage of who received at least one dose of vaccine and later got reinfected equaled 7.3%. This small rate may indicate that a small number of people become reinfected after vaccination due to the efficiency of these vaccines, as several studies in Qatar have demonstrated [303-305]. Eleven cases were reinfected after 14 days from being fully vaccinated, which could indicate a breakthrough infection (getting infected even after receiving two doses of vaccine), as multiple studies have shown that full immunity develops after 14 days from full vaccination [306-309].

Symptomatic status of reinfection

In this study, symptomatic status of reinfected cases accounted for 39% of all reinfected, while rates in England were slightly lower, accounting for 32% [88]. The rates were higher in some studies which was found to be 50% in a study conducted in the USA [310], 74% in Czech Republic [98], and 72% in France [106]. The low number of symptomatic cases during reinfection in Qatar can be attributed to the population's younger age which is associated with being healthier, or it could be linked to the fact

that different definitions of asymptomatic cases are used, resulting in disparities in reporting [311]. Thirty one percent of patients who had no symptoms in the first infection developed symptoms in reinfection indicating less severity of reinfection, unlike other studies showing more aggressive reinfection [106]. Half of reinfected children and adolescents with the age of 18 years and below in our study had symptoms in the first infection, while 36% had symptoms in both episodes. A study in Qatar divulges that the prevalence of symptoms in infected children with similar age group were equal to 36.6% [312].

Combined practices were both strong protective factors against symptomatic status of reinfection. Consistent with our findings, a study conducted in Switzerland among young adults showed that stringent social distancing and hygiene were suggestive to be associated with reducing the rate of symptoms of patients infected with COVID-19 [313]. These two measures may be associated with reducing the viral inoculum during infection, leading to reduction of cases developing symptoms when reinfected with COVID-19 [313]. This finding may support the hypothesis that performing multiple preventive measures always may reduce the dose of the virus when reinfected, leading to milder and asymptomatic infection manifestations [314]. These findings could point to the possible link between viral dosage and illness severity.

According to the findings of this study, those who had symptoms during the first infection are more likely to have symptoms in reinfection. This finding is especially meaningful because a first infection is not possibly providing protection against a second infection. Explanations include short-term immune system protection, or enhancement of the immune system [315, 316], resulting in a manifestation development in the second infection. Hospitalization during the first infection was also associated with symptomatic status of reinfection indicating severity of the illness.

These findings could point to a reinfection with an aggressive SARS-CoV-2 variant, which would cause symptoms and, in some cases, severe illness. Patients arriving in Qatar from diverse countries were found to be reinfected with distinct SARS-CoV-2 strains throughout a time span that was somewhat identical to our study [317], which could explain the clinical course and hospitalization in reinfected individuals. Even though cases with severe disease may have higher antibody levels that are still detectable two to three months after primary infection, data was not available on the symptom's severity in reinfection, leading to the conclusion that more information is required to fully understand this association.

Time interval between the first and second infections

The interval between the first and second episodes had median of 309 days, as other studies in Czech Republic [98] and England [88] showed that the median time intervals were 201.5 days and 201 days, respectively. This may show that reinfection mainly occurs after a long median time from the first infection, as may indicate a long immune protection against reinfection after natural infection. For instance, herein we reported that always practicing all preventive measures, and never engaging in any of risk practices were strongly associated with longest time interval until reinfection. This may imply that the practice of combined multiple preventive practices and avoidance of any risk practice has an influence on protecting or prolonging the time until reinfection.

Symptomatic status of the first infection was found to be associated with shorter time interval until reinfection. In support to these findings, a study found that cases with severe symptoms in the first infection had lower median days between the two episodes compared to those with non-severe symptoms [318]. This could indicate that who experienced symptoms during the first infection might have had a weak immune system

that provided only short-term protection. Comorbidities or immunosuppressed individuals, which were not explored in this study, could be explanations for the low immunity, making them more prone to be reinfected . Hospitalization status of the first infection was found to be associated with longest time interval until reinfection. As an explanation, those who were hospitalized in the first infection might have triggered higher production of antibodies, consequently leading to long-term protection against reinfection [79].

According to several epidemiological studies, natural immunity protection from reinfection occurs for at least 6–12 months [88, 89, 100, 290, 319], while other studies conducted in UK and USA showed less duration of protection after natural infection (5-7 months) [319-322]. Short-term protection against reinfection was also observed reaching between 2 to 3 months as presented in a study conducted in China [80]. Because of the complexity of immune responses, protection duration is heterogenous between individuals [323], and possible explanations for this disparity may include the fact that the length of immune system protection against a new infection is affected by various parameters, including the strain, age of primary infection, and illness severity [324]. Understanding factors influencing persistence of antibodies and protection after natural infection or vaccination is essential to provide better understanding the variation in time intervals to reinfection between individuals.

Other study findings

Laith Abu Raddad and colleagues did several investigations on SARS-CoV-2 reinfection in Qatar [265]. The first was a cohort study that attempted to analyze the risk and incidence rate of reinfected cases in Qatar by utilizing a time interval of 45 days or more between infections as criteria for determining reinfection [265]. Further sensitivity analysis for the risk of reinfection was conducted in reinfected cases after 60

days from the initial infection, and whole genome sequencing was performed to confirm the reinfection [265]. Another cohort study conducted by the same author utilized the latter criteria for reinfected cases [267]. The study aimed to assess the risk and incidence of reinfection in an anti-body positive cases followed up for more than seven months from primary infection. Findings showed no evidence for possible waning of immunity after being infected with COVID-19 and the protection against reinfection from natural infection was equal to 95% [267].

While the latter studies followed up patients and determined the incidence and risk of reinfection, the current study is complementary to these studies in that we investigated the characteristics of the reinfected cases and considered epidemiological aspects such as preventive and risk practices in relation to developing symptoms during reinfection and the time interval between the first and second infections. Moreover, the criteria used for determining reinfected cases in our study (i.e. time interval of at least 90 days between the two infections) was based on a comprehensive literature review conducted in Chapter 3, while initial Abu Raddad's study included reinfected cases after at least 45 days [265].

Two cases were found to meet the developed criteria for confirmed reinfected cases (Chapter 3: p.36) with a three-month interval until reinfection, at least 3 negative PCR tests with one month duration until the first negative test. Although we found only 2 relevant cases meeting the criteria developed in the scoping review, this might raise some questions regarding missing some identified reinfected cases. There are multiple body mechanisms that occur which might be misinterpreted as something else rather that reinfection. The criteria devised were created with the sole purpose of reinfection and how is it differs from these mechanisms. This low number of reinfected cases could be due to the use of time interval as a case definition for reinfection, with no

investigation of other aspects (e.g. number and duration of negative tests after the first infection), which could have effectively ruled out many of those who had reinfection, resulting in underestimation. Furthermore, there are no guidelines in Qatar requiring infected patients to be followed up on or to undergo continuous screening to ensure viral clearance from the body and to detect all reinfected cases.

Data analysis challenges

For each model developed, relevant assumptions were tested. 'Time interval' had non-normally distributed residuals and did not show homoscedasticity (constant variance) for the linear regression assumptions. As a result, box-cox transformation was considered since it is a widely used method when assumptions are violated, as it also showed normally distributed residuals, however, due to complexity of statistical methods for back-transformation for the aim of interpretation, other methods were used. Later, a quantile regression model was developed, which compares associations between factors and various time interval distributions using different quantiles. However, a problem with a very wide confidence interval has surfaced, which could indicate low precision in estimates, leading to erroneous conclusions.

Finally, ordinal logistic regression was examined, as well as the proportional odds assumption. In practice, the data frequently violates the proportional odds assumption. In our case, the brant model indicated some variables to be violating this assumption; however, no violation was found when evaluating the final models. Furthermore, a generalized ordered logit model was created and compared to the ordinal regression model using AIC and BIC tests to determine which model fit data better. The results demonstrated that the ordinal regression model is more fit of the data, and thus it was used in the analysis. Ordinal logistic regression is far more parsimonious than multinomial logistic regression models, which are sometimes incorrectly used

when this assumption is violated [287]. In addition, ordinal logistic regression was utilized since it is a robust method that is advised when a continuous outcome is skewed [325]. It is also more preferred when compared to dichotomous or multinomial categorization which have several statistical implications including the power of the study [326].

Limitations and strengths

It is essential to recognize limitations of the study. First, possible reasons that may cause an underestimation of reinfected cases are: limited follow-up testing, lack of surveillance system for asymptomatic infections, and not seeking medical care or receive diagnosis when mild or no symptoms appear [327, 328]. People also tended to travel in summer (study period: March to June 2021) after lockdown for two years which may have led to lower chances of capturing the true number of reinfected cases.

Second, there is a lack of a clear definition of asymptomatic infection, as well as probability of misclassification of those in the pre-symptomatic phase, as they may show no symptoms at that stage of the disease and were later not followed up on for confirmation of symptoms. This might consequence in misclassification of symptomatic as asymptomatic cases, and possibly resulting in an overestimation of the rate of asymptomatic reinfected cases [43].

Third, while our findings suggest that preventive practices and not participating in risk practices are associated with a longer time interval until reinfection, the true reason, including biological mechanisms, has not been studied, so we do not know whether immune protection played a role in extending this period or not.

Fourth, the presence of symptoms in reinfection may correlate with other factors not measured in our study including existing health conditions such as cardiovascular diseases, lung diseases, hypertension and diabetes, and cancer [329].

Fifth, it is important to note that it is not possible to eliminate residual confounding even after adjusting for known and measured confounders in the multivariable models.

Sixth, some variables such as symptomatic status and practices after the first infection were self-reported by patients during case investigation, as this might introduce measurement and recall bias.

Seventh, because the investigation of reinfected cases began in March 2021 and the study was completed in August 2021, reinfected cases included were within this period, which is considered relatively short. For better outcomes, we recommend designing research with a longer time frame or develop follow-up studies.

Lastly, majority of cases were reinfected after 9-months from the first infection and this could be due to the start of investigation of reinfected cases in March 2021, therefore, missing many reinfected cases with shorter time duration. For this reasons, the categorization of time interval outcome investigated was based upon quantiles. Although quantile categorization is not ideal, it was the best option given the available data.

Notwithstanding the limitations, according to our knowledge, this is the first study to investigate retrospectively analyzed factors associated with symptomatic status of reinfection and time period until reinfection in the region. Not only focusing on specific types of variables, this study also explored at a variety of demographic, practice, and clinical factors to examine what could be explaining the development of symptomatic status of reinfection. Despite the fact that this is a cross-sectional study with a short data collection period, the analysis was done retrospectively, indicating that the temporal association may hold. This study also included all investigated SARS-CoV-2 reinfection cases between March and June 2021; however, more follow-up

studies are needed to be able to generalize findings of all reinfected cases in Qatar.

Implications

This study has several implications. The study's findings will assist clinicians in better understanding the various characteristics of reinfected cases when diagnosing and providing treatments. It will also guide healthcare professionals while developing promotion programs to encourage preventive practices and dissuade risk practices as well as countries in developing guidelines and regulations for individual public health measures. Findings will also help in the preparation of such measures in upcoming big sports event such as the 2022 FIFA World Cup Qatar. Understanding reinfection of the disease is necessary for the prevention and preparedness of the upsurge of reinfection and infection rates in Qatar during this big event.

Recommendations

Even if efficacious and safe vaccination have developed, individual public health measures is needed to continue its ongoing role in combating outbreaks and in curtailing the virus transmission in the country. The use of preventive practices is critical in recovered patients and should be emphasized, particularly among healthcare workers who are more vulnerable. We propose that additional research will potentially generate insights relevant for more understanding of reinfection in Qatar prioritizing strategies to decrease the impact of the epidemic, as well as performing qualitative research on possible reasons for those not practicing preventive measures and engaged in risk practices after the first infection. Some studies showed that data on serology tests and sequencing is needed to be further studied to gain a better understanding of the evolution of symptomatic status of reinfection and time interval until reinfection among different regions. More research into time to reinfection is needed in order to properly estimate results when utilizing a continuous outcome such as survival analysis. Furthermore, the majority of patients were reinfected after more than 9 months,

implying that protection from a prior infection may continue a long time, and more research on the duration of protection against reinfection is required. Governments communicating with the public on benefits of preventive measures to achieve high level of public compliance.

Conclusion

In conclusion, we provided description of reinfected cases as findings presented in this study which underlines the value of promoting individual level public health measures through mandating them among the public through the development of policies. We evaluated whether engaging in preventive and neglecting risk practices is associated with the development of COVID-19 symptoms during reinfection, as well as the effect on time until reinfection. Our main findings indicate that all combined preventive practices and all non-performed risk practices are associated with asymptomatic status of reinfection as well as a longer time to reinfection. In order to draw conclusions on causal relationships, more robust follow-up research are necessary.

REFERENCES

1. Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. Int J Surg. 2020;78:185-93.

2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta bio-medica : Atenei Parmensis. 2020;91(1):157-60.

3. Cunningham CH, Stuart HO. Cultivation of the virus of infectious bronchitis of chickens in embryonated chicken eggs. Am J Vet Res. 1947;8(27):209-12.

4. Almeida JD, Tyrrell DA. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. J Gen Virol. 1967;1(2):175-8.

5. ViralZone. Coronavirinae. . Available from: https://viralzone.expasy.org/785

6. Subissi L, Posthuma CC, Collet A, Zevenhoven-Dobbe JC, Gorbalenya AE, Decroly E, et al. One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(37):E3900-9.

7. Lambeir AM, Durinx C, Scharpé S, De Meester I. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV. Critical reviews in clinical laboratory sciences. 2003;40(3):209-94.

8. Chu H, Zhou J, Wong BH, Li C, Cheng ZS, Lin X, et al. Productive replication of Middle East respiratory syndrome coronavirus in monocyte-derived dendritic cells modulates innate immune response. Virology. 2014;454-455:197-205.

9. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nature reviews Microbiology. 2009;7(6):439-50.

10. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virology journal. 2019;16(1):69.

11. Vlasova AN, Zhang X, Hasoksuz M, Nagesha HS, Haynes LM, Fang Y, et al. Two-way antigenic cross-reactivity between severe acute respiratory syndrome coronavirus (SARS-CoV) and group 1 animal CoVs is mediated through an antigenic site in the N-terminal region of the SARS-CoV nucleoprotein. Journal of virology. 2007;81(24):13365-77.

12. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ (Clinical research ed). 2020;368:m606.

13. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. . Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

14. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging microbes & infections. 2020;9(1):221-36.

15. World Health Organization. Coronavirus disease (COVID-19). 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/336034/nCoV-weekly-sitrep11Oct20-eng.pdf.

16. Cornish D. Epidemiology and Its Role in COVID-19. Available from: https://coe.uni.edu/epidemiology-and-its-role-covid-19.

17. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2021. Available from: https://covid19.who.int/?gclid=EAIaIQobChMIkazL-ojJ8gIVjpGyCh1iEgKXEAAYASABEgKf9_D_BwE.

18. Johns Hopkins University Center for Systems Science and Engineering. COVID-19 Dashboard. 2021. Available from: https://coronavirus.jhu.edu/map.html.

19. Sorci G, Faivre B, Morand S. Explaining among-country variation in COVID-19 case fatality rate. Scientific Reports. 2020;10(1):18909.

20. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for Covid-19 severity and fatality: a structured literature review. Infection. 2021;49(1):15-28.

21. Ho FK, Celis-Morales CA, Gray SR, Katikireddi SV, Niedzwiedz CL, Hastie C, et al. Modifiable and non-modifiable risk factors for COVID-19, and comparison to risk factors for influenza and pneumonia: results from a UK Biobank prospective cohort study. BMJ Open. 2020;10(11):e040402.

22. Khan TM. Preventive and Control Measures of COVID-19 Patients: A Review. Bangladesh Journal of Infectious Diseases. 2020;1(suppl_1):S41-S4.

23. Nussbaumer-Streit B, Mayr V, Dobrescu A, Chapman A, Persad E, Klerings I, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. Cochrane Database of Systematic Reviews. 2020(4).

24. Tian H, Liu Y, Li Y, Wu CH, Chen B, Kraemer MUG, et al. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. Science (New York, NY). 2020;368(6491):638-42.

25. Wang M-Y, Zhao R, Gao L-J, Gao X-F, Wang D-P, Cao J-M. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. Front Cell Infect Microbiol. 2020;10:587269-.

26. Coronavirus (COVID-19) Vaccinations [Internet]. University of Oxford. 2021. Available from: https://ourworldindata.org/covid-vaccinations.

27. Holder J. Tracking Coronavirus Vaccinations Around the World. The new york times. 2021.

28. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Al Kanaani Z, Al Khal A, Al Kuwari E, et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. Scientific Reports. 2021;11(1):6233.

29. MoPH confirms second wave in Qatar due to new strains, failure to adhere to previous rules. QLNews. 2021.

30. World Health Organization. A report on Qatar's national response to COVID-19. 2021.

31. Al Khal A, Al-Kaabi S, Checketts RJ. Qatar's Response to COVID-19 Pandemic. Heart Views. 2020;21(3):129-32.

32. Osterrieder A, Cuman G, Pan-Ngum W, Cheah PK, Cheah P-K, Peerawaranun P, et al. Economic and social impacts of COVID-19 and public health measures: results from an anonymous online survey in Thailand, Malaysia, the UK, Italy and Slovenia. BMJ Open. 2021;11(7):e046863.

33. Schwartz DA, Graham AL. Potential Maternal and Infant Outcomes from Coronavirus 2019-nCoV (SARS-CoV-2) Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. 2020;12(2):194.

34. Centers for disease control and prevention. Delta Variant: What We Know About the Science. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html.

35. Pal M, Berhanu G, Desalegn C, Kandi V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus. 2020;12(3):e7423-e.

36. Adhanom Ghebreyesus T. Addressing mental health needs: an integral part of COVID-19 response. World Psychiatry. 2020;19(2):129-30.

37. Koçak O, Koçak ÖE, Younis MZ. The Psychological Consequences of COVID-19 Fear and the Moderator Effects of Individuals' Underlying Illness and Witnessing Infected Friends and Family. 2021;18(4):1836.

38. Brooks S, Webster R, Smith L, Woodland L, Wessely S, Greenberg N, et al. The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence. SSRN Electronic Journal. 2020;395.

39. Chen S, Igan DO, Pierri N, Presbitero AF, Soledad M, Peria M. Tracking the Economic Impact of COVID-19 and Mitigation Policies in Europe and the United States. IMF Working Papers. 2020;2020(125):A001.

40. Beutels P, Jia N, Zhou QY, Smith R, Cao WC, de Vlas SJ. The economic impact of SARS in Beijing, China. Tropical medicine & international health : TM & IH. 2009;14 Suppl 1:85-91.

41. OECD. Strengthening the frontline: How primary health care helps health systems adapt during the COVID 19 pandemic. 2021. Available from: https://www.oecd.org/coronavirus/policy-responses/strengthening-the-frontline-how-primary-health-care-helps-health-systems-adapt-during-the-covid-19-pandemic-9a5ae6da/.

42. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. 2020;12(4):372.

43. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection. Annals of Internal Medicine. 2020;173(5):362-7.

44. Rajaraman S, Antani S. Weakly Labeled Data Augmentation for Deep Learning: A Study on COVID-19 Detection in Chest X-Rays. 2020;10(6):358.

45. World Health Organization. Update 1.4 Clinical Management of COVID-19: Living Guidance. 2021. Available from: https://app.magicapp.org/#/guideline/j1WBYn/rec/EalkPn.

46. Baerheim A. The diagnostic process in general practice: has it a two-phase structure? Family Practice. 2001;18(3):243-5.

47. Wu SY, Yau HS, Yu MY, Tsang HF, Chan LWC, Cho WCS, et al. The diagnostic methods in the COVID-19 pandemic, today and in the future. Expert Review of Molecular Diagnostics. 2020;20(9):985-93.

48. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases.2020. Available from: https://www.who.int/publications/i/item/10665-331501.

49. Centers for disease control and prevention. Nucleic Acid Amplification Tests (NAATs). 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/naats.html.

50. Centers for disease control and prevention. Interim Guidelines for Collecting and Handling of Clinical Specimens for COVID-19 Testing. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html.

51. Das A, Ahmed R, Akhtar S, Begum K, Banu S. An overview of basic molecular biology of SARS-CoV-2 and current COVID-19 prevention strategies. Gene Rep. 2021;23:101122-.

52. Bullis SSM, Crothers JW, Wayne S, Hale AJ. A cautionary tale of false-negative nasopharyngeal COVID-19 testing. IDCases. 2020;20:e00791.

53. World Health Organization. Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities. 2021.

54. Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerging microbes & infections. 2020;9(1):386-9.

55. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(16):2027-34.

56. Sun B, Feng Y, Mo X, Zheng P, Wang Q, Li P, et al. Kinetics of SARS-CoV-2 specific IgM and IgG responses in COVID-19 patients. Emerging microbes & infections. 2020;9(1):940-8.

57. Alhajj M, Farhana A. Enzyme Linked Immunosorbent Assay. StatPearls. Treasure Island (FL): StatPearls Publishing

58. Hanif M, Haider MA, Ali MJ, Naz S, Sundas F. Reinfection of COVID-19 in Pakistan: A First Case Report. Cureus. 2020;12(10):e11176.

59. American College of Radiology. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. 2020. Available from: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection.

60. Wong HYF, Lam HYS, Fong AH-T, Leung ST, Chin TW-Y, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. Radiology. 2020;296(2):E72-E8.

61. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic:

A Multinational Consensus Statement from the Fleischner Society. Radiology. 2020;296(1):172-80.

62. Cerutti F, Burdino E, Milia MG, Allice T, Gregori G, Bruzzone B, et al. Urgent need of rapid tests for SARS CoV-2 antigen detection: Evaluation of the SD-Biosensor antigen test for SARS-CoV-2. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2020;132:104654.

63. Vandenberg O, Martiny D, Rochas O, van Belkum A, Kozlakidis Z. Considerations for diagnostic COVID-19 tests. Nature Reviews Microbiology. 2021;19(3):171-83.

64. COVID-19 Genomics UK Consortium. What do virologists mean by 'mutation', 'variant' and 'strain'?. 2021. Available from: https://www.cogconsortium.uk/what-do-virologists-mean-by-mutation-variant-and-strain/.

65. Lauring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2—What Do They Mean? Jama. 2021;325(6):529-31.

66. Centers for disease control and prevention. What is Genomic Surveillance?. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-surveillance.html.

67. Salehi-Vaziri M, Omrani MD, Pouriayevali MH, Fotouhi F, Banifazl M, Farahmand B, et al. SARS-CoV-2 presented moderately during two episodes of the infection with lack of antibody responses. Virus research. 2021;299:198421-.

68. Zucman N, Uhel F, Descamps D, Roux D, Ricard JD. Severe reinfection with South African SARS-CoV-2 variant 501Y.V2: A case report. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021.

69. World Health Organization. Tracking SARS-CoV-2 variants. 2021. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.

70. Institute for Quality and Efficiency in Health Care (IQWiG). The innate and adaptive immune systems. 2006. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279396/.

71. Forthal DN. Functions of Antibodies. Microbiol Spectr. 2014;2(4):1-17.

72. American Society for Microbiology. COVID-19 Serology Testing Explained2020. Available from: https://asm.org/Articles/2020/May/COVID-19-Serology-Testing-Explained.

73. Wajnberg A, Mansour M, Leven E, Bouvier NM, Patel G, Firpo-Betancourt A, et al. Humoral response and PCR positivity in patients with COVID-19 in the New York City region, USA: an observational study. The Lancet Microbe. 2020;1(7):e283-e9.

74. Guthmiller JJ, Stovicek O, Wang J, Changrob S, Li L, Halfmann P, et al. SARS-CoV-2 Infection Severity Is Linked to Superior Humoral Immunity against the Spike. 2021;12(1):e02940-20.

75. Wu J, Liang B, Chen C, Wang H, Fang Y, Shen S, et al. SARS-CoV-2 infection induces sustained humoral immune responses in convalescent patients following symptomatic COVID-19. Nature Communications. 2021;12(1):1813.

76. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet. 2021;397(10270):220-32.

77. Arkhipova-Jenkins I, Helfand M, Armstrong C, Gean E, Anderson J, Paynter RA, et al. Antibody Response After SARS-CoV-2 Infection and Implications for Immunity. Annals of Internal Medicine. 2021;174(6):811-21.

78. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science (New York, NY). 2021;371(6529).

79. Seow J, Graham C, Merrick B, Acors S, Pickering S, Steel KJA, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nature Microbiology. 2020;5(12):1598-607.

80. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nature Medicine. 2020;26(8):1200-4.

81. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-62.

82. Krajewski R, Gołębiowska J, Makuch S, Mazur G, Agrawal S. Update on serologic testing in COVID-19. Clinica chimica acta; international journal of clinical chemistry. 2020;510:746-50.

83. Luo A. Positive SARS-Cov-2 test in a woman with COVID-19 at 22 days after hospital discharge: A case report. Journal of Traditional Chinese Medical Sciences. 2020;7(4):413-7.

84. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(15):778-85.

85. Chao YX, Rötzschke O, Tan EK. The role of IgA in COVID-19. Brain, behavior, and immunity. 2020;87:182-3.

86. Fox A, Marino J, Amanat F, Krammer F, Hahn-Holbrook J, Zolla-Pazner S, et al. Evidence of a significant secretory-IgA-dominant SARS-CoV-2 immune response in human milk following recovery from COVID-19. medRxiv : the preprint server for health sciences. 2020:2020.05.04.20089995.

87. Harvey RA, Rassen JA, Kabelac CA, Turenne W, Leonard S, Klesh R, et al. Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection. JAMA Internal Medicine. 2021;181(5):672-9.

88. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). The Lancet. 2021;397(10283):1459-69.

89. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. The Lancet. 2021;397(10280):1204-12.

90. Chivese T, Matizanadzo JT, Musa OAH, Hindy G, Furuya-Kanamori L, Islam N, et al. The prevalence of adaptive immunity to COVID-19 and reinfection after recovery – a comprehensive systematic review and meta-analysis of 12 011 447 individuals. medRxiv : the preprint server for health sciences. 2021:2021.09.03.21263103.

91. Tirado SM, Yoon KJ. Antibody-dependent enhancement of virus infection and disease. Viral immunology. 2003;16(1):69-86.

92. Reinfection with COVID-19 [Internet]. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/your-health/reinfection.html.

93. Teka IA, BenHasan MH, Alkershini AA, Alatresh OK, Abulifa TA, Lembagga HA, et al. Reinfection with SARS-CoV-2: A case report from Libya. Travel medicine and infectious disease. 2021;41:102040.

94. AlFehaidi A, Ahmad SA, Hamed E. SARS-CoV-2 re-infection: a case report from Qatar. J Infect. 2021;82(3):414-51.

95. To KK-W, Hung IF-N, Ip JD, Chu AW-H, Chan W-M, Tam AR, et al. Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing. Clinical Infectious Diseases. 2020.

96. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. The Lancet Infectious Diseases. 2021;21(1):52-8.

97. Inada M, Ishikane M, Terada M, Matsunaga A, Maeda K, Tsuchiya K, et al. Asymptomatic COVID-19 re-infection in a Japanese male by elevated half-maximal inhibitory concentration (IC₅₀) of neutralizing antibodies. Journal of Infection and Chemotherapy. 2021;27(7):1063-7.

98. Fabiánová K, Kynčl J, Vlčková I, Jiřincová H, Košťálová J, Liptáková M, et al. COVID-19 reinfections. Epidemiologie, mikrobiologie, imunologie : casopis Spolecnosti pro epidemiologii a mikrobiologii Ceske lekarske spolecnosti JE Purkyne. 2021;70(1):62-7.

99. Habadi MI, Balla Abdalla TH, Hamza N, Al-Gedeei A. COVID-19 Reinfection. Cureus. 2021;13(1):e12730-e.

100. Leidi A, Koegler F, Dumont R, Dubos R, Zaballa ME, Piumatti G, et al. Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-

score matched cohort study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021.

101. Sofian M, Velayati AA, Banifazl M, Fotouhi F, Sadat Larijani M, Afzali N, et al. SARS-CoV-2, a virus with many faces: a series of cases with prolonged persistence of COVID-19 symptoms. Wiener Medizinische Wochenschrift. 2021;171(1):3-6.

102. Yadav SP, Wadhwa T, Thakkar D, Kapoor R, Rastogi N, Sarma S. COVID-19 reinfection in two children with cancer. Pediatric hematology and oncology. 2021;38(4):403-5.

103. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death & Differentiation. 2020;27(5):1451-4.

104. García LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. Frontiers in immunology. 2020;11:1441.

105. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

106. Brouqui P, Colson P, Melenotte C, Houhamdi L, Bedotto M, Devaux C, et al. COVID-19 re-infection. European Journal of Clinical Investigation. 2021;51(5):e13537.

107. Mukherjee A, Anand T, Agarwal A, Singh H, Chatterjee P, Narayan J, et al. SARS-CoV-2 re-infection: development of an epidemiological definition from India. Epidemiol Infect. 2021;149:e82-e.

108. Zhao W, Wang Y, Tang Y, Zhao W, Fan Y, Liu G, et al. Characteristics of Children With Reactivation of SARS-CoV-2 Infection After Hospital Discharge. Clinical Pediatrics. 2020;59(9-10):929-32.

109. World Health Organization. Criteria for releasing COVID-19 patients from isolation. 2020. Available from: https://www.who.int/news-room/commentaries/detail/criteria-for-releasing-covid-19-patients-from-isolation.

110. World Health Organization. Laboratory testing of human suspected cases of novel coronavirus (nCoV) infection.2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/330374/WHO-2019-nCoV-laboratory-2020.1-eng.pdf.

111. Coyle PV, Molawi NHA, Kacem MABH, Kahlout RAE, Kuwari EA, Khal AA, et al. Inclusion of cycle threshold (CT) values when reporting SARS-CoV-2 RT-PCR results improves clinical Interpretation in suspected and confirmed COVID-19. medRxiv : the preprint server for health sciences. 2021:2021.02.11.21251557.

112. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2020;25(32):2001483.

113. Zheng J, Zhou R, Chen F, Tang G, Wu K, Li F, et al. Incidence, clinical course and risk factor for recurrent PCR positivity in discharged COVID-19 patients in Guangzhou, China: A prospective cohort study. PLoS neglected tropical diseases. 2020;14(8):e0008648.

114. Shui T-J, Li C, Liu H-b, Chen X, Zhang B-k. Characteristics of recovered COVID-19 patients with recurrent positive RT-PCR findings in Wuhan, China: a retrospective study. BMC Infectious Diseases. 2020;20(1):749.

115. Yang C, Jiang M, Wang X, Tang X, Fang S, Li H, et al. Viral RNA level, serum antibody responses, and transmission risk in recovered COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study. Emerging microbes & infections. 2020;9(1):2368-78.

116. The Association of Public Health Laboratories. Ct Values: What They Are and How They Can be Used. 2021.

117. Boldogh I, Albrecht T, Porter D. Persistent Viral Infections. In: 4th, editor. Medical Microbiology. Galveston, Texas: University of Texas Medical Branch at Galveston; 1996.

118. Kang H, Wang Y, Tong Z, Liu X. Retest positive for SARS-CoV-2 RNA of "recovered" patients with COVID-19: Persistence, sampling issues, or re-infection? Journal of medical virology. 2020;92(11):2263-5.

119. Traylen CM, Patel HR, Fondaw W, Mahatme S, Williams JF, Walker LR, et al. Virus reactivation: a panoramic view in human infections. Future Virol. 2011;6(4):451-63.

120. Stöppler MC. Definition of relapse. 2021. Available from: https://www.rxlist.com/relapse/definition.htm.

121. MacIntyre CR, Chughtai AA. Recurrence and reinfection—a new paradigm for the management of Ebola virus disease. International Journal of Infectious Diseases. 2016;43:58-61.

122. Yao W, Hertel L, Wahl LM. Dynamics of recurrent viral infection. Proc Biol Sci. 2006;273(1598):2193-9.

123. Zhou L, Liu K, Liu HG. [Cause analysis and treatment strategies of "recurrence" with novel coronavirus pneumonia (COVID-19) patients after discharge from hospital]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2020;43(4):281-4.

124. Liang L, Guo Q, Zhang H, Lin S, Zheng H, Li B, et al. Low infectious risk of re-positive COVID-19 patients: a single-center study. International Journal of Infectious Diseases. 2021;111:5-9.

125. Daudt HM, van Mossel C, Scott SJ. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. BMC Med Res Methodol. 2013;13:48.

126. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Annals of Internal Medicine. 2018;169(7):467-73.

127. Centers for Disease Control and Prevention. Interim Guidance on Ending Isolation and Precautions for Adults with COVID-19. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html.

128. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

129. The EndNote Team. Endnote. EndNote X9 ed. Philadelphia, PA: Clarivate; 2013.

130. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

131. World Health Organization. COVID-19 Clinical management: living guidance. 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1.

132. National Institutes of Health. Quality Assessment Tool for Case Series. 2014. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

133. Wells G, Shea B, O'Connell D, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

134. Heylen L, Oris E, Wollants E, Maes P, Van Kerrebroeck M, Peeters J, et al. 128 days of SARS-CoV-2 viral shedding in a haemodialysis patient. Clin Kidney J. 2021;14(4):1284-6.

135. Jain A, Kaur J, Rai AK, Pandey AK. Anosmia: A Clinical Indicator of COVID-19 Reinfection. Ear, Nose and Throat Journal. 2021;100(2_suppl):180S-1S.

136. Inada M, Ishikane M, Terada M, Matsunaga A, Maeda K, Tsuchiya K, et al. Asymptomatic COVID-19 re-infection in a Japanese male by elevated half-maximal inhibitory concentration (IC50) of neutralizing antibodies. Journal of Infection and Chemotherapy. 2021.

137. Yadav SP, Thakkar D, Bhoyar R, Jain A, Wadhwa Arora T, Imran M, et al. Asymptomatic reactivation of SARS-CoV-2 in a child with neuroblastoma characterised by whole genome sequencing. IDCases. 2020;23:30326-33.

138. Gupta V, Bhoyar RC, Jain A, Srivastava S, Upadhayay R, Imran M, et al. Asymptomatic Reinfection in 2 Healthcare Workers From India With Genetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2. Clinical Infectious Diseases. 2020.

139. Becky Mingyao MA, Hung IFN, Chan GCW, Tam AR, Chan SSK, Wong BCK, et al. Case of “relapsing” COVID-19 in a kidney transplant recipient. Nephrology. 2020;25(12):933-6.

140. Mohseni M, Albus M, Kaminski A, Harrison MF. A Case of COVID-19 Re-Infection in a Liver Transplant Patient. Cureus. 2021;13(5).

141. Sicsic Jr I, Chacon AR, Zaw M, Ascher K, Abreu A, Chediak A. A case of SARS-CoV-2 reinfection in a patient with obstructive sleep apnea managed with telemedicine. BMJ Case Reports. 2021;14(2).

142. Prado-Vivar B, Becerra-Wong M, Guadalupe JJ, Márquez S, Gutierrez B, Rojas-Silva P, et al. A case of SARS-CoV-2 reinfection in Ecuador. The Lancet Infectious Diseases. 2020.

143. Dou C, Xie X, Peng Z, Tang H, Jiang Z, Zhong Z, et al. A case presentation for positive SARS-CoV-2 RNA recurrence in a patient with a history of type 2 diabetes that had recovered from severe COVID-19. Diabetes research and clinical practice. 2020;166:108300-.

144. Caralis P. Case Reports of COVID 19 Recurrence. Journal of Primary Care and Community Health. 2021;12.

145. Zhao W, Wang Y, Tang Y, Zhao W, Fan Y, Liu G, et al. Characteristics of Children With Reactivation of SARS-CoV-2 Infection After Hospital Discharge. Clin Pediatr (Phila). 2020;59(9-10):929-32.

146. Tie-Jun S, Li C, Hong-bing L, Chen X, Bi-ke Z. Characteristics of recovered COVID-19 patients with recurrent positive RT-PCR findings in Wuhan, China: a retrospective study. BMC Infectious Diseases. 2020;20:1-7.

147. Wu J, Xiao-ying X, He-lei L, Xia H, Wen-xiang H, Jia B, et al. Clinical characteristics and outcomes of discharged COVID-19 patients with reoccurrence of SARS-CoV-2 RNA. Future Virol. 2020;15(10):663-–71.

148. He S, Zhou K, Hu M, Liu C, Xie L, Sun S, et al. Clinical characteristics of "re-positive" discharged COVID-19 pneumonia patients in Wuhan, China. Scientific Reports. 2020;10(1).

149. Pan L, Wang R, Yu N, Hu C, Yan J, Zhang X, et al. Clinical characteristics of re-hospitalized COVID-19 patients with recurrent positive SARS-CoV-2 RNA: a retrospective study. European Journal of Clinical Microbiology and Infectious Diseases. 2021;40(6):1245-52.

150. Zhou J, Zhang J, Zhou J, Yi H, Lin Z, Liu Y, et al. Clinical characteristics of re-positive COVID-19 patients in Huangshi, China: A retrospective cohort study. PloS one. 2020;15(11).

151. Ye G, Pan Z, Pan Y, Deng Q, Chen L, Li J, et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. J Infect. 2020;80(5):e14-e7.

152. Chen J, Xu XP, Hu J, Chen QD, Xu FF, Liang H, et al. Clinical course and risk factors for recurrence of positive SARS-CoV-2 RNA: a retrospective cohort study from Wuhan, China. Aging-Us. 2020;12(17):16675-89.

153. Lu J, Peng J, Xiong Q, Liu Z, Lin H, Tan X, et al. Clinical, immunological and virological characterization of COVID-19 patients that test re-positive for SARS-CoV-2 by RT-PCR. EBioMedicine. 2020;59:102960.

154. Shastri J, Parikh S, Agrawal S, Chatterjee N, Pathak M, Chaudhary S, et al. Clinical, Serological, Whole Genome Sequence Analyses to Confirm SARS-CoV-2 Reinfection in Patients From Mumbai, India. Frontiers in Medicine. 2021;8.

155. Vetter P, Cordey S, Schibler M, Vieux L, Despres L, Laubscher F, et al. Clinical, virologic and immunologic features of a mild case of SARS-CoV-2 reinfection. Clin Microbiol Infect. 2021;27(5):791.e1-4.

156. Liu Y, Ding N, Zhou S, Chen C, Huang S, Lv Y, et al. Comparison of clinical characteristics between patients with Coronavirus disease 2019 (COVID-19) who retested RT-PCR positive versus negative: A retrospective study of data from Nanjing. Journal of Thoracic Disease. 2020;12(11):6435-45.

157. Harrington D, Kele B, Pereira S, Couto-Parada X, Riddell A, Forbes S, et al. Confirmed Reinfection with SARS-CoV-2 Variant VOC-202012/01. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021.

158. Ozaras R, Ozdogru I, Yilmaz AA. Coronavirus disease 2019 re-infection: first report from Turkey. New Microbes and New Infections. 2020;38.

159. Brouqui P, Colson P, Melenotte C, Houhamdi L, Bedotto M, Devaux C, et al. COVID-19 re-infection. Eur J Clin Invest. 2021;51(5):e13537.

160. To KK, Hung IF, Ip JD, Chu AW, Chan WM, Tam AR, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis. 2020.

161. Gulati K, Prendecki M, Clarke C, Willicombe M, McAdoo S. COVID-19 Reinfection in a Patient Receiving Immunosuppressive Treatment for Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis & Rheumatology. 2021;73(6):1091-2.

162. Bongiovanni M, Marra AM, Bini F, Bodini BD, Carlo DD, Giuliani G. COVID-19 reinfection in healthcare workers: A case series. Journal of Infection. 2021;82(6):e4-e5.

163. Yadav SP, Wadhwa T, Thakkar D, Kapoor R, Rastogi N, Sarma S. COVID-19 reinfection in two children with cancer. Pediatric hematology and oncology. 2021;38(4):403-5.

164. Fabiánová K, Kynčl J, Vlčková I, Jiřincová H, Košťálová J, Liptáková M, et al. Covid-19 reinfections. Epidemiologie, Mikrobiologie, Imunologie. 2021;70(1):62-7.

165. Chew C, Mannepalli S. COVID-19: No Guaranteed Protection from Future Infection after the Initial Diagnosis. Case Reports in Infectious Diseases. 2021;2021.

166. Garvey MI, Casey AL, Wilkinson MAC, Ratcliffe L, McMurray C, Stockton J, et al. Details of SARS-CoV-2 reinfections at a major UK tertiary centre. Journal of Infection. 2021;82(6):e29-e30.

167. Siqueira JD, Goes LR, Alves BM, da Silva ACP, de Carvalho PS, Cicala C, et al. Distinguishing SARS-CoV-2 bonafide re-infection from pre-existing minor variant reactivation. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2021;90:104772.

168. Salzer HJF. Emerging COVID-19 reinfection four months after primary SARS-CoV-2 infection. Wiener Medizinische Wochenschrift. 2021.

169. Peltan ID, Beesley SJ, Webb BJ, Lopansri BK, Sinclair W, Jacobs JR, et al. Evaluation of potential COVID-19 recurrence in patients with late repeat positive SARS-CoV-2 testing. PloS one. 2021;16(5 May).

170. Colson P, Finaud M, Levy N, Lagier JC, Raoult D. Evidence of SARS-CoV-2 re-infection with a different genotype. Journal of Infection. 2021;82(4):84-123.

171. Sevillano G, Ortega-Paredes D, Loaiza K, Zurita-Salinas C, Zurita J. Evidence of SARS-CoV-2 reinfection within the same clade in Ecuador: A case study. Int J Infect Dis. 2021;108:53-6.

172. Lee JS, Kim SY, Kim TS, Hong KH, Ryoo NH, Lee J, et al. Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection After Recovery from Mild Coronavirus Disease 2019. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.

173. Bellanti F, Lo Buglio A, Custodero G, Barbera L, Minafra G, Montrano M, et al. Fatal relapse of COVID-19 after recovery? A case report of an older Italian patient. Journal of Infection. 2021;82(1):e49-e51.

174. Novoa W, Miller H, Mattar S, Faccini-Martínez ÁA, Rivero R, Serrano-Coll H. A first probable case of SARS-CoV-2 reinfection in Colombia. Annals of Clinical Microbiology and Antimicrobials. 2021;20(1).

175. Okar L, Ahmad R, Yassin MA. First report of COVID-19 reinfection in a patient with beta thalassemia major. Clin Case Rep. 2021;9(2):861-5.

176. Bader A, Hassan A, Moussa M, Alsaif HS, Alfaraj D. Fulminant hepatic failure in a patient testing re-positive for SARS-CoV-2: a case report. International Journal of Emergency Medicine (Online). 2021;14(1).

177. Fintelman-Rodrigues N, da Silva APD, Dos Santos MC, Saraiva FB, Ferreira MA, Gesto J, et al. Genetic Evidence and Host Immune Response in Persons Reinfected with SARS-CoV-2, Brazil. Emerg Infect Dis. 2021;27(5):1446-53.

178. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis. 2021;21(1):52-8.

179. Fonseca V, de Jesus R, Adelino T, Reis AB, de Souza BB, Ribeiro AA, et al. Genomic evidence of SARS-CoV-2 reinfection case with the emerging B.1.2 variant in Brazil. The Journal of infection. 2021:5126-.

180. Zheng J, Zhou R, Chen F, Tang G, Wu K, Li F, et al. Incidence, clinical course and risk factor for recurrent pcr positivity in discharged covid-19 patients in guangzhou, china: A prospective cohort study. PLoS neglected tropical diseases. 2020;14(8):1-14.

181. Duggan NM, Ludy SM, Shannon BC, Reisner AT, Wilcox SR. Is novel coronavirus 2019 reinfection possible? Interpreting dynamic SARS-CoV-2 test results. American Journal of Emergency Medicine. 2021;39:256.e1-.e3.

182. Coppola A, Annunziata A, Carannante N, Di Spirito V, Fiorentino G. Late Reactivation of SARS-CoV-2: A Case Report. Front Med (Lausanne). 2020;7:531.

183. Bentivegna E, Sentimentale A, Luciani M, Speranza ML, Guerritore L, Martelletti P. New IgM seroconversion and positive RT-PCR test after exposure to the virus in recovered COVID-19 patient. Journal of medical virology. 2021;93(1):97-8.

184. Tuan J, Spichler-Moffarah A, Onyema O. A new positive SARS-CoV-2 test months after severe COVID-19 illness: reinfection or intermittent viral shedding? BMJ Case Reports. 2021;14(2).

185. Sharma R, Sardar S, Mohammad Arshad A, Ata F, Zara S, Munir W. A Patient with Asymptomatic SARS-CoV-2 Infection Who Presented 86 Days Later with COVID-19 Pneumonia Possibly Due to Reinfection with SARS-CoV-2. Am J Case Rep. 2020;21:e927154.

186. Yang JR, Deng DT, Wu N, Yang B, Li HJ, Pan XB. Persistent viral RNA positivity during the recovery period of a patient with SARS-CoV-2 infection. J Med Virol. 2020;92(9):1681-3.

187. Sook Yin L, Bassett J, Hoodless EJ, Walshaw M. Possible COVID-19 reinfection in a patient with X-linked agammaglobulinaemia. BMJ Case Reports. 2021;14(3).

188. Wong J, Koh WC, Momin RN, Alikhan MF, Fadillah N, Naing L. Probable causes and risk factors for positive SARS-CoV-2 test in recovered patients: Evidence from Brunei Darussalam. Journal of medical virology. 2020;92(11):2847-51.

189. Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: Not a rare phenomenon. J Med Virol. 2020;92(11):2286-7.

190. Fageeh H, Alshehri A, Fageeh H, Bizzoca ME, Lo Muzio L, Quadri MFA. Re-infection of SARS-CoV-2: A case in a young dental healthcare worker. Journal of Infection and Public Health. 2021;14(6):685-8.

191. Ravioli S, Ochsner H, Lindner G. Reactivation of COVID-19 pneumonia: A report of two cases. J Infect. 2020;81(2):e72-e3.

192. Leung S, Hossain N. Recurrence and Recovery of COVID-19 in an Older Adult Patient with Multiple Comorbidities: A Case Report. Gerontology. 2021.

193. Loconsole D, Passerini F, Palmieri VO, Centrone F, Sallustio A, Pugliese S, et al. Recurrence of COVID-19 after recovery: a case report from Italy. Infection. 2020;48(6):965-7.

194. Vassallo C, Pupo F, Marri L, Schiavi C, Giusti F, Greco M, et al. Recurrence of COVID-19 related symptoms and viral detection in a patient discharged after complete recovery and test negativization. Italian Journal of Medicine. 2021;15(1).

195. Alonso FOM, Sabino BD, Guimarães M, Varella RB. Recurrence of SARS-CoV-2 infection with a more severe case after mild COVID-19, reversion of RT-qPCR for positive and late antibody response: Case report. J Med Virol. 2021;93(2):655-6.

196. Shoar S, Khavandi S, Tabibzadeh E, Khavandi S, Naderan M, Shoar N. Recurrent coronavirus diseases 19 (COVID-19): A different presentation from the first episode. Clinical Case Reports. 2021;9(4):2149-52.

197. Liu T, Wu S, Zeng G, Zhou F, Li Y, Guo F, et al. Recurrent positive SARS-CoV-2: Immune certificate may not be valid. Journal of Medical Virology. 2020;92(11):2384-6.

198. Nepal R, Sapkota K, Gurung S, Paudel P, Neupane P, Sah KK. Recurrent positivity of SARS-CoV-2 RNA in a clinically recovered COVID-19 patient with end-stage renal disease: A case report. Journal of the Nepal Medical Association. 2020;58(231):918-22.

199. Salcin S, Fontem F. Recurrent SARS-CoV-2 infection resulting in acute respiratory distress syndrome and development of pulmonary hypertension: A case report. Respir Med Case Rep. 2021;33:101314.

200. Torres DdA, Ribeiro LdCB, Riello APdFL, Horovitz DDG, Pinto LFR, Croda J. Reinfection of COVID-19 after 3 months with a distinct and more aggressive clinical presentation: Case report. Journal of Medical Virology. 2021;93(4):1857-9.

201. Hanif M, Haider MA, Ali MJ, Naz S, Sundas FNU. Reinfection of COVID-19 in Pakistan: A First Case Report. Cureus. 2020;12(10).

202. Ibrahim M, Vegel A, Niu A, Panse K, Chen R, Safah H, et al. Reinfection versus failure of viral clearance in a COVID-19 patient with hematologic malignancy. Leukemia Research. 2021;101.

203. Marquez L, Koy T, Spinler JK, Luna RA, Tocco L, Fasciano L, et al. Reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.7 variant in an immunocompromised adolescent. Infect Control Hosp Epidemiol. 2021:1-2.

204. Radhakrishnan V, Gangopadhyay D. Repeat-positive SARS-CoV-2 in a child with cancer. Pediatric Blood and Cancer. 2021;68(3).

205. Liu F, Cai Z-B, Huang J-S, Niu H-Y, Yu W-Y, Zhang Y, et al. Repeated COVID-19 relapse during post-discharge surveillance with viral shedding lasting for 67 days in a recovered patient infected with SARS-CoV-2. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2021;54(1):101-4.

206. Amorim MR, Souza WM, Barros ACG, Toledo-Teixeira DA, Bispo-Dos-Santos K, Simeoni CL, et al. Respiratory viral shedding in healthcare workers reinfected with SARS-CoV-2, Brazil, 2020. Emerging Infectious Diseases. 2021;27(6):1737-40.

207. Peng D, Zhang J, Ji Y, Pan D. Risk factors for redetectable positivity in recovered COVID-19 children. Pediatric Pulmonology. 2020;55(12):3602-9.

208. Hong LX, Liu L, Lin A, Yan WH. Risk factors for SARS-CoV-2 re-positivity in COVID-19 patients after discharge. International Immunopharmacology. 2021;95.

209. Novazzi F, Baj A, Genoni A, Spezia PG, Colombo A, Cassani G, et al. SARS-CoV-2 B.1.1.7 reinfection after previous COVID-19 in two immunocompetent Italian patients. Journal of medical virology. 2021.

210. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). The Lancet. 2021;397(10283):1459-69.

211. Li J, Long X, Fang X, Zhang Q, Hu S, Lin Z, et al. SARS-CoV-2 positivity in a discharged COVID-19 patient: a case report. Clinical Microbiology and Infection. 2020;26(8):1115-7.

212. Salehi-Vaziri M, Omrani MD, Pouriayevali MH, Fotouhi F, Banifazl M, Farahmand B, et al. SARS-CoV-2 presented moderately during two episodes of the infection with lack of antibody responses. Virus Research. 2021;299.

213. Mukherjee A, Anand T, Agarwal A, Singh H, Chatterjee P, Narayan J, et al. SARS-CoV-2 re-infection: development of an epidemiological definition from India. Epidemiology and Infection. 2021;149.

214. Brehm TT, Pfefferle S, von Possel R, Kobbe R, Nörz D, Schmiedel S, et al. SARS-CoV-2 Reinfection in a Healthcare Worker Despite the Presence of Detectable Neutralizing Antibodies. Viruses. 2021;13(4).

215. Zhang K, Yiu-Nam Lau J, Yang L, Ma ZG. SARS-CoV-2 reinfection in two patients who have recovered from COVID-19. Precision Clinical Medicine. 2020;3(4):292-3.

216. Fernandes AC, Figueiredo R. SARS-CoV-2 reinfection: A case report from Portugal. Revista da Sociedade Brasileira de Medicina Tropical. 2021;54.

217. Wan XF, Tang CY, Ritter D, Wang Y, Li T, Segovia K, et al. SARS-CoV-2 show no infectivity at later stages in a prolonged COVID-19 patient despite positivity in RNA testing. J Med Virol. 2021;93(7):4570-5.

218. Reuken PA, Stallmach A, Pletz MW, Brandt C, Andreas N, Hahnfeld S, et al. Severe clinical relapse in an immunocompromised host with persistent SARS-CoV-2 infection. Leukemia. 2021;35(3):920-3.

219. Selvaraj VMD, Herman KMD, Dapaah-Afriyie KMD. Severe, Symptomatic Reinfection in a Patient with COVID-19. Rhode Island Medical Journal. 2020;103(10):29-31.

220. Hu J, Li S, Wu Y, Xiong Z, Yang Y, Gong L, et al. Surveillance and re-positive RNA test in patients recovered from COVID-19. Journal of medical virology. 2021;93(3):1221-4.

221. Atici S, Ek ÖF, Yildiz MS, Şikgenç MM, Güzel E, Soysal A. Symptomatic recurrence of SARS-CoV-2 infection in healthcare workers recovered from COVID-19. Journal of Infection in Developing Countries. 2021;15(1):69-72.

222. Rani PR, Imran M, Lakshmi JV, Jolly B, Jain A, Surekha A, et al. Symptomatic reinfection of SARS-CoV-2 with spike protein variant N440K associated with immune escape. Journal of Medical Virology. 2021;93(7):4163-5.

223. Tian M, Long Y, Hong Y, Zhang X, Zha Y. The treatment and follow-up of 'recurrence' with discharged COVID-19 patients: data from Guizhou, China. Environmental Microbiology. 2020;22(8):3588-92.

224. Ye H, Zhao C, Yang L, Yu W, Leng Z, Sun Y, et al. Twelve out of 117 recovered COVID-19 patients retest positive in a single-center study of China. EClinicalMedicine. 2020;26.

225. Abu-Raddad LJ, Chemaitelly H, Malek JA, Ahmed AA, Mohamoud YA, Younuskunju S, et al. Two prolonged viremic SARS-CoV-2 infections with conserved viral genome for two months. Infection, Genetics and Evolution. 2021;88.

226. Chen W, Hu Z, Yi C, Chi Y, Xiong Q, Tan CW, et al. An unusual COVID-19 case with over four months of viral shedding in the presence of low neutralizing antibodies: a case report. Journal of Biomedical Research. 2020;34(6):470-4.

227. Yang C, Jiang M, Wang XH, Tang XJ, Fang SS, Li H, et al. Viral RNA level, serum antibody responses, and transmission risk in recovered COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study. Emerging Microbes & Infections. 2020;9(1):2368-78.

228. Chen J, Xu X, Hu J, Chen Q, Xu F, Liang H, et al. Clinical course and risk factors for recurrence of positive SARS-CoV-2 RNA: a retrospective cohort study from Wuhan, China. Aging. 2020;12(17):16675-89.

229. Tian M, Long Y, Hong Y, Zhang X, Zha Y. The treatment and follow-up of 'recurrence' with discharged COVID-19 patients: data from Guizhou, China. Environmental microbiology. 2020;22(8):3588-92.

230. Bonifácio LP, Pereira APS, Araújo DCdAE, Balbão VdMP, Fonseca BALd, Passos ADC, et al. Are SARS-CoV-2 reinfection and Covid-19 recurrence possible? a case report from Brazil. Revista da Sociedade Brasileira de Medicina Tropical. 2020;53:e20200619-e.

231. Masiá M, Padilla S, Galiana A, Fernández-González M, Gutiérrez F. Incidence of delayed asymptomatic COVID-19 recurrences in a 6-month longitudinal study. Journal of Infection. 2021;82(6):276-316.

232. Krishna VN, Ahmad M, Overton ET, Jain G. Recurrent COVID-19 in Hemodialysis: A Case Report of 2 Possible Reinfections. Kidney Medicine. 2021;3(3):447-50.

233. Salehi-Vaziri M, Jalali T, Farahmand B, Fotouhi F, Banifazl M, Pouriayevali MH, et al. Clinical characteristics of SARS-CoV-2 by re-infection vs. reactivation: a case series from Iran. European Journal of Clinical Microbiology & Infectious Diseases. 2021.

234. Tehrani HA, Darnahal M, Nadji SA, Haghighi S. COVID-19 re-infection or persistent infection in patient with acute myeloid leukaemia M3: a mini review. New Microbes and New Infections. 2021;39:100830.

235. Sen MK, Gupta N, Yadav SR, Kumar R, Singh B, Ish P. Contentious Issue in Recurrent COVID-19 Infection: Reactivation or Reinfection. Turkish thoracic journal. 2020;21(6):463-6.

236. Song K-H, Kim D-M, Lee H, Ham SY, Oh S-M, Jeong H, et al. Dynamics of viral load and anti-SARS-CoV-2 antibodies in patients with positive RT-PCR results after recovery from COVID-19. The Korean journal of internal medicine. 2021;36(1):11-4.

237. Ahmed A, Sana F, Ikram A, Yousaf S, Khan A. Reinfection or relapse of COVID-19 in health care workers; case series of 2 patients from Pakistan. New Microbes and New Infections. 2021;42:100896.

238. He F, Luo Q, Lei M, Fan L, Shao X, Hu K, et al. Successful recovery of recurrence of positive SARS-CoV-2 RNA in COVID-19 patient with systemic lupus erythematosus: a case report and review. Clin Rheumatol. 2020;39(9):2803-10.

239. Harvey RA, Rassen JA, Kabelac CA, Turenne W, Leonard S, Klesh R, et al. Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection. JAMA Intern Med. 2021;181(5):672-9.

240. Van Damme W, Dahake R, van de Pas R, Vanham G, Assefa Y. COVID-19: Does the infectious inoculum dose-response relationship contribute to understanding heterogeneity in disease severity and transmission dynamics? Med Hypotheses. 2021;146:110431-.

241. Sim BLH, Chidambaram SK, Wong XC, Pathmanathan MD, Peariasamy KM, Hor CP, et al. Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: A nationwide observational study. The Lancet Regional Health – Western Pacific. 2020;4.

242. Hunsinger DHP, Kutti Sridharan DG, Rokkam DVRP, Fantry DLE. COVID-19 Reinfection in An Immunosuppressed Patient Without An Antibody Response. Am J Med Sci. 2021;362(1):103-.

243. Drancourt M, Cortaredona S, Melenotte C, Amrane S, Eldin C, La Scola B, et al. SARS-CoV-2 Persistent Viral Shedding in the Context of Hydroxychloroquine-Azithromycin Treatment. 2021;13(5):890.

244. Fu Y, Han P, Zhu R, Bai T, Yi J, Zhao X, et al. Risk Factors for Viral RNA Shedding in COVID-19 Patients. European Respiratory Journal. 2020:2001190.

245. Munker D, Osterman A, Stubbe H, Muenchhoff M, Veit T, Weinberger T, et al. Dynamics of SARS-CoV-2 shedding in the respiratory tract depends on the severity of disease in COVID-19 patients. European Respiratory Journal. 2021;58(1):2002724.

246. Chen Z, Xie W, Ge Z, Wang Y, Zhao H, Wang J, et al. Reactivation of SARS-CoV-2 infection following recovery from COVID-19. Journal of Infection and Public Health. 2021;14(5):620-7.

247. Tang X, Musa SS, Zhao S, He D. Reinfection or Reactivation of Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. 2021;9(593).

248. Yahav D, Yelin D, Eckerle I, Eberhardt CS, Wang J, Cao B, et al. Definitions for coronavirus disease 2019 reinfection, relapse and PCR re-positivity. Clin Microbiol Infect. 2021;27(3):315-8.

249. Sterlin D, Mathian A, Miyara M, Mohr A, Anna F, Claër L, et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. Science translational medicine. 2021;13(577):eabd2223.

250. Yu H-q, Sun B-q, Fang Z-f, Zhao J-c, Liu X-y, Li Y-m, et al. Distinct features of SARS-CoV-2-specific IgA response in COVID-19 patients. European Respiratory Journal. 2020:2001526.

251. Petersen LR, Sami S, Vuong N, Pathela P, Weiss D, Morgenthau BM, et al. Lack of Antibodies to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a Large Cohort of Previously Infected Persons. Clinical Infectious Diseases. 2021;73(9):e3066-e73.

252. Townsend JP, Hassler HB, Wang Z, Miura S, Singh J, Kumar S, et al. The durability of immunity against reinfection by SARS-CoV-2: a comparative evolutionary study. The Lancet Microbe.

253. Maemura T, Kuroda M, Armbrust T, Yamayoshi S, Halfmann PJ, Kawaoka Y, et al. Antibody-Dependent Enhancement of SARS-CoV-2 Infection Is Mediated by the IgG Receptors FcγRIIA and FcγRIIIA but Does Not Contribute to Aberrant Cytokine Production by Macrophages. 2021;12(5):e01987-21.

254. Jefferson T, Spencer EA, Brassey J, Heneghan C. Viral Cultures for Coronavirus Disease 2019 Infectivity Assessment: A Systematic Review. Clinical Infectious Diseases. 2020.

255. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. N Engl J Med. 2020;383(23):2291-3.

256. Centers for disease control and prevention. Investigative Criteria for Suspected Cases of SARS-CoV-2 Reinfection (ICR). 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html#print.

257. Mukherjee A, Anand T, Agarwal A, Singh H, Chatterjee P, Narayan J, et al. SARS-CoV-2 re-infection: development of an epidemiological definition from India. Epidemiol Infect. 2021;149:e82.

258. Raveendran AV. COVID-19 re-infection: Diagnostic challenges and proposed diagnostic criteria. Diabetes Metab Syndr. 2021;15(2):645-8.

259. Tomassini S, Kotecha D, Bird PW, Folwell A, Biju S, Tang JW. Setting the criteria for SARS-CoV-2 reinfection - six possible cases. J Infect. 2021;82(2):282-327.

260. Pinto LM, Nanda V, Sunavala A, Rodriques C. Reinfection in COVID-19: A scoping review. Med J Armed Forces India. 2021;77(Suppl 2):S257-S63.

261. Babiker A, Marvil CE, Waggoner JJ, Collins MH, Piantadosi A. The Importance and Challenges of Identifying SARS-CoV-2 Reinfections. Journal of clinical microbiology. 2021;59(4):e02769-20.

262. Bentivegna E, Sentimentale A, Luciani M, Speranza ML, Guerritore L, Martelletti P. New IgM seroconversion and positive RT-PCR test after exposure to the virus in recovered COVID-19 patient. Journal of medical virology. 2021;93(1):97-8.

263. Prado-Vivar B, Becerra-Wong M, Guadalupe JJ, Márquez S, Gutierrez B, Rojas-Silva P, et al. A case of SARS-CoV-2 reinfection in Ecuador. The Lancet Infectious Diseases. 2021;21(6):e142.

264. Harrington D, Kele B, Pereira S, Couto-Parada X, Riddell A, Forbes S, et al. Confirmed Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variant VOC-202012/01. Clinical Infectious Diseases. 2021.

265. Abu-Raddad LJ, Chemaitelly H, Malek JA, Ahmed AA, Mohamoud YA, Younuskunju S, et al. Assessment of the risk of SARS-CoV-2 reinfection in an

intense re-exposure setting. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.

266. Vitale J, Mumoli N, Clerici P, De Paschale M, Evangelista I, Cei M, et al. Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy. JAMA Internal Medicine. 2021.

267. Abu-Raddad LJ, Chemaitelly H, Coyle P, Malek JA, Ahmed AA, Mohamoud YA, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. EClinicalMedicine. 2021;35.

268. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLOS Medicine. 2020;17(9):e1003346.

269. Alene M, Yismaw L, Assemie MA, Ketema DB, Mengist B, Kassie B, et al. Magnitude of asymptomatic COVID-19 cases throughout the course of infection: A systematic review and meta-analysis. PloS one. 2021;16(3):e0249090.

270. Gandhi M, Beyrer C, Goosby E. Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-CoV-2 to Protect the Wearer. J Gen Intern Med. 2020;35(10):3063-6.

271. Gandhi M, Rutherford GW. Facial Masking for Covid-19 - Potential for "Variolation" as We Await a Vaccine. N Engl J Med. 2020;383(18):e101-e.

272. Lio CF, Cheong HH, Lei CI, Lo IL, Yao L, Lam C, et al. Effectiveness of personal protective health behaviour against COVID-19. BMC Public Health. 2021;21(1):827.

273. Deressa W, Worku A, Abebe W, Getachew S, Amogne W. Social distancing and preventive practices of government employees in response to COVID-19 in Ethiopia. PloS one. 2021;16(9):e0257112.

274. Imai M, Iwatsuki-Horimoto K, Hatta M, Loeber S, Halfmann PJ, Nakajima N, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proceedings of the National Academy of Sciences of the United States of America. 2020;117(28):16587-95.

275. Murphy BR, Clements ML, Madore HP, Steinberg J, O'Donnell S, Betts R, et al. Dose response of cold-adapted, reassortant influenza A/California/10/78 virus (H1N1) in adult volunteers. The Journal of infectious diseases. 1984;149(5):816.

276. Murphy BR, Clements ML, Tierney EL, Black RE, Stienberg J, Chanock RM. Dose response of influenza A/Washington/897/80 (H3N2) avian-human reassortant virus in adult volunteers. The Journal of infectious diseases. 1985;152(1):225-9.

277. Han A, Czajkowski LM, Donaldson A, Baus HA, Reed SM, Athota RS, et al. A Dose-finding Study of a Wild-type Influenza A(H3N2) Virus in a Healthy Volunteer Human Challenge Model. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;69(12):2082-90.

278. Watson JM, Francis JN, Mesens S, Faiman GA, Makin J, Patriarca P, et al. Characterisation of a wild-type influenza (A/H1N1) virus strain as an experimental challenge agent in humans. Virology journal. 2015;12:13.

279. Guallar MP, Meiriño R, Donat-Vargas C, Corral O, Jouvé N, Soriano V. Inoculum at the time of SARS-CoV-2 exposure and risk of disease severity. International Journal of Infectious Diseases. 2020;97:290-2.

280. Hains DS, Schwaderer AL, Carroll AE, Starr MC, Wilson AC, Amanat F, et al. Asymptomatic Seroconversion of Immunoglobulins to SARS-CoV-2 in a Pediatric Dialysis Unit. Jama. 2020;323(23):2424-5.

281. Cline S. Cases at seafood plant cause spike in Oregon COVID numbers. 2020. Available from: https://www.newsbreak.com/news/1581086288035/cases-at-seafood-plant-cause-spike-in-oregon-covid-numbers.

282. Erinoso O, Wright K, Anya S, Bowale A, Adejumo O, Adesola S, et al. Clinical characteristics, predictors of symptomatic coronavirus disease 2019 and duration of hospitalisation in a cohort of 632 Patients in Lagos State, Nigeria. 2020;27(4):285-92.

283. Textor J, Hardt J, Knüppel S. DAGitty A Graphical Tool for Analyzing Causal Diagrams. Epidemiology (Cambridge, Mass). 2011;22:745.

284. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48.

285. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Medical Research Methodology. 2008;8(1):70.

286. Shrestha N. Detecting Multicollinearity in Regression Analysis. American Journal of Applied Mathematics and Statistics. 2020;8:39-42.

287. Williams R. Generalized Ordered Logit/Partial Proportional Odds Models for Ordinal Dependent Variables. The Stata Journal. 2006;6(1):58-82.

288. StataCorp. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC; 2021.

289. Flacco ME, Acuti Martellucci C, Soldato G, Carota R, Fazii P, Caponetti A, et al. Rate of reinfections after SARS-CoV-2 primary infection in the population of an Italian province: a cohort study. Journal of Public Health. 2021.

290. Vitale J, Mumoli N, Clerici P, De Paschale M, Evangelista I, Cei M, et al. Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy. JAMA Intern Med. 2021.

291. Zare F, Teimouri M, Khosravi A, Rohani-Rasaf M, Chaman R, Hosseinzadeh A, et al. COVID-19 re-infection in Shahroud, Iran: a follow-up study. Epidemiol Infect. 2021;149:e159.

292. World population review. Qatar Population 2021 (Live). 2020. Available from: https://worldpopulationreview.com/countries/qatar-population.

293. Al Jazeera Media Network. Qatar reimposes coronavirus-related restrictions. Al Jazeera Media Network. 2021.

294. Hussain S. 70% of population must receive COVID-19 vaccine to protect community: expert. 2020. Available from: https://www.dohanews.co/70-of-population-must-receive-covid-19-vaccine-to-protect-community-expert/.

295. Ministry of Public Health. Information tailored for you. 2021. Available from: https://covid19.moph.gov.qa/EN/Information-tailored-for-you/Pages/default.aspx.

296. Knoema. Qatar - Male to female ratio of the total population. 2020. Available from: https://knoema.com/atlas/Qatar/topics/Demographics/Population/Male-to-female-ratio.

297. Gulf Labour Markets and Migration. Demography, Migration, and the Labour Market in Qatar. 2017.

298. Al-Hanawi MK, Angawi K, Alshareef N, Qattan AMN, Helmy HZ, Abudawood Y, et al. Knowledge, Attitude and Practice Toward COVID-19 Among the Public in the Kingdom of Saudi Arabia: A Cross-Sectional Study. Front Public Health. 2020;8:217-.

299. Weiss Barry D, Paasche-Orlow Michael K. Disparities in Adherence to COVID-19 Public Health Recommendations. HLRP: Health Literacy Research and Practice. 2020;4(3):e171-e3.

300. Pirhadi R, Sinai Talaulikar V, Onwude J, Manyonda I. Could Estrogen Protect Women From COVID-19? J Clin Med Res. 2020;12(10):634-9.

301. Gadi N, Wu SC, Spihlman AP, Moulton VR. What's Sex Got to Do With COVID-19? Gender-Based Differences in the Host Immune Response to Coronaviruses. Frontiers in immunology. 2020;11:2147.

302. Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, et al. Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. EClinicalMedicine. 2020;29.

303. Abu-Raddad L, Chemaitelly H, Ayoub H, Yassine H, Benslimane F, Khatib H, et al. Protection afforded by the BNT162b2 and mRNA-1273 COVID-19 vaccines in fully vaccinated cohorts with and without prior infection2021.

304. Abu-Raddad LJ, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, et al. Pfizer-BioNTech mRNA BNT162b2 Covid-19 vaccine protection against variants of concern after one versus two doses. Journal of travel medicine. 2021;28(7).

305. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021;27(9):1614-21.

306. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Yassine HM, Benslimane FM, Al Khatib HA, et al. Association of Prior SARS-CoV-2 Infection With Risk of

Breakthrough Infection Following mRNA Vaccination in Qatar. Jama. 2021;326(19):1930-9.

307. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.

308. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.

309. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021.

310. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection Rates Among Patients Who Previously Tested Positive for Coronavirus Disease 2019: A Retrospective Cohort Study. Clinical Infectious Diseases. 2021.

311. Trunfio M, Longo BM, Alladio F, Venuti F, Cerutti F, Ghisetti V, et al. On the SARS-CoV-2 “Variolation Hypothesis”: No Association Between Viral Load of Index Cases and COVID-19 Severity of Secondary Cases. 2021;12(473).

312. Musa OAH, Chivese T, Bansal D, Abdulmajeed J, Ameen O, Islam N, et al. Prevalence and determinants of symptomatic COVID-19 infection among children and adolescents in Qatar: a cross-sectional analysis of 11 445 individuals. Epidemiol Infect. 2021;149:e193.

313. Bielecki M, Züst R, Siegrist D, Meyerhofer D, Crameri GAG, Stanga Z, et al. Social Distancing Alters the Clinical Course of COVID-19 in Young Adults: A Comparative Cohort Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;72(4):598-603.

314. Zhang S, Guo M, Wu F, Xiong N, Ma Y, Wang Z, et al. Factors associated with asymptomatic infection in health-care workers with severe acute respiratory syndrome coronavirus 2 infection in Wuhan, China: a multicentre retrospective cohort study. Clinical Microbiology and Infection. 2020;26(12):1670-5.

315. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JC, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. eLife. 2020;9.

316. Larson D, Brodniak SL, Voegtly LJ, Cer RZ, Glang LA, Malagon FJ, et al. A Case of Early Re-infection with SARS-CoV-2. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.

317. Bertollini R, Chemaitelly H, Yassine HM, Al-Thani MH, Al-Khal A, Abu-Raddad LJ. Associations of Vaccination and of Prior Infection With Positive PCR Test Results for SARS-CoV-2 in Airline Passengers Arriving in Qatar. Jama. 2021;326(2):185-8.

318. Murillo-Zamora E, Mendoza-Cano O, Delgado-Enciso I, Hernandez-Suarez CM. Predictors of severe symptomatic laboratory-confirmed SARS-CoV-2 reinfection. Public Health. 2021;193:113-5.

319. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. N Engl J Med. 2021;384(6):533-40.

320. Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. Lancet (London, England). 2020;396(10262):1595-606.

321. Hall V, Foulkes S, Charlett A, Atti A, Monk E, Simmons R, et al. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody

negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 20202021.

322. Ripperger TJ, Uhrlaub JL, Watanabe M, Wong R, Castaneda Y, Pizzato HA, et al. Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low-Prevalence Communities and Reveal Durable Humoral Immunity. Immunity. 2020;53(5):925-33.e4.

323. Reynolds CJ, Swadling L, Gibbons JM, Pade C, Jensen MP, Diniz MO, et al. Discordant neutralizing antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection. Sci Immunol. 2020;5(54):eabf3698.

324. Krishna E, Pathak VK, Prasad R, Jose H, Kumar MM. COVID-19 reinfection: Linked Possibilities and future outlook. J Family Med Prim Care. 2020;9(11):5445-9.

325. Liu Q, Shepherd BE, Li C, Harrell FE, Jr. Modeling continuous response variables using ordinal regression. Stat Med. 2017;36(27):4316-35.

326. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ (Clinical research ed). 2006;332(7549):1080-.

327. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect. 2020;53(3):404-12.

328. Wu SL, Mertens AN, Crider YS, Nguyen A, Pokpongkiat NN, Djajadi S, et al. Substantial underestimation of SARS-CoV-2 infection in the United States. Nat Commun. 2020;11(1):4507.

329. Honardoost M, Janani L, Aghili R, Emami Z, Khamseh ME. The Association between Presence of Comorbidities and COVID-19 Severity: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases. 2021;50(2):132-40.

330. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama. 2012;307(23):2526-33.

331. Khemani RG, Smith LS, Zimmerman JJ, Erickson S. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2015;16(5 Suppl 1):S23-40.

332. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, et al. Hospital Incidence and Outcomes of the Acute Respiratory Distress Syndrome Using the Kigali Modification of the Berlin Definition. American journal of respiratory and critical care medicine. 2016;193(1):52-9.

333. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Medicine. 2017;43(3):304-77.

334. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2020;21(2):e52-e106.

335. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.

APPENDICES

Appendix A: Search strategy

Table A 1. Search Strategy Built and Number of Articles According to Each Database

#	Search strategy	Number of results
Pubmed		
#1	(((((((("COVID-19"[Title]) OR ("Covid19"[Title])) OR ("corona virus"[Title])) OR ("SARS-CoV-2"[Title])) OR ("Severe acute respiratory syndrome coronavirus 2"[Title])) OR ("2019nCoV"[Title])) OR ("2019 nCoV"[Title])) OR ("2019-nCoV"[Title])) OR ("HCoV-19"[Title])) OR (coronavirus[MeSH Terms])	136,332
#2	((((((((((((((("Reinfection"[Title/Abstract]) OR ("re-infection"[Title/Abstract])) OR ("re-positive"[Title/Abstract])) OR ("relapse"[Title/Abstract])) OR ("repositive"[Title/Abstract])) OR ("recurrence"[Title/Abstract])) OR ("recurrent"[Title/Abstract])) OR ("late presentation"[Title/Abstract])) OR ("delayed presentation"[Title/Abstract])) OR ("retested positive"[Title/Abstract])) OR ("persistence"[Title/Abstract])) OR ("Reactivation"[Title/Abstract])) OR ("Re-activation"[Title/Abstract])) OR ("re-tested positive"[Title/Abstract])) OR ("reoccurrence"[Title/Abstract])) OR ("re-occurrence"[Title/Abstract])) OR ("post infection"[Title/Abstract])) OR ("postinfection"[Title/Abstract]) OR ("post-infection"[Title/Abstract]) OR ("repositive"[Title/Abstract]) OR ("re-tested positive"[Title/Abstract])	827,460
#3	((((((("whole genome sequencing") OR ("seroconversion")) OR ("sero-conversion")) OR ("antibody response")) OR ("immune response")) OR ("viral strain")) OR ("viral clade") OR ("variant")	423,886
#4	(#1) AND (#2) AND (#3)	**287**
Embase		
#1	('covid-19':ti OR 'covid19':ti OR 'corona virus':ti OR 'sars-cov-2':ti OR 'severe acute respiratory syndrome 2':ti OR '2019ncov':ti OR '2019 ncov':ti OR '2019-ncov':ti OR 'hcov-19':ti OR 'coronavirus':ti OR 'coronavirus disease 2019':ti)	126,230
#2	('reinfection':ti,ab,kw OR 're-infection':ti,ab,kw OR 're-positive':ti,ab,kw OR 'relapse':ti,ab,kw OR 'recurrence':ti,ab,kw OR 'recurrent':ti,ab,kw OR 'late presentation':ti,ab,kw OR 'delayed presentation':ti,ab,kw OR 'retested positive':ti,ab,kw OR 'persistence':ti,ab,kw	1,184,269

	OR 'postinfection':ti,ab,kw OR 'post-infection':ti,ab,kw OR 'repositive':ti,ab,kw OR 're-tested-positive':ti,ab,kw) 'reinfection' OR 're-infection' OR 're-positive' OR 'relapse' OR 'recurrence' OR 'recurrent' OR 'late presentation' OR 'delayed presentation' OR 'retested positive' OR 'persistence' OR 'postinfection' OR 'post-infection' OR 'repositive' OR 're-tested-positive'	
#3	'whole genome sequencing' OR 'seroconversion' OR 'sero-conversion' OR 'antibody response' OR 'immune response' OR 'viral clade' OR 'viral strain' OR 'variant'	769,133
#4	#1 AND #2 AND #3	**325**
Scopus		
	(TITLE ((covid-19) OR (covid19) OR (corona virus) OR (SARS-CoV-2) OR (Severe acute respiratory syndrome coronavirus 2) OR (2019nCoV) OR (2019 nCoV) OR (2019-nCoV) OR (HCoV-19) OR (coronavirus)) TITLE-ABS-KEY ((reinfection) OR (re-infection) OR (re-positive) OR (relapse) OR (repositive) OR (recurrence) OR (recurrent) OR (late presentation) OR (delayed presentation) OR (retested positive) OR (persistence) OR (Reactivation) OR (Re-activation) OR (re-tested positive) OR (reoccurrence) OR (re-occurrence) OR (post infection) OR (postinfection) OR (post-infection) OR (repositive) OR (re-tested positive)) ALL ((whole genome sequencing) OR (seroconversion) OR (sero-conversion) OR (antibody response) OR (immune response) OR (viral strain) OR (viral clade) OR (variant))	**1615**
Web of Science		
#1	TI=("covid-19" OR "covid19" OR "corona virus" OR "SARS-CoV-2" OR "Severe acute respiratory syndrome coronavirus 2" OR "2019nCoV" OR "2019 nCoV" OR "2019-nCoV" OR "HCoV-19" OR "coronavirus")	122,699
#2	AB=("Reinfection" OR "re-infection" OR "re-positive" OR "relapse" OR "repositive" OR "recurrence" OR "recurrent" OR "late presentation" OR "delayed presentation" OR "retested positive" OR "persistence" OR "Reactivation" OR "Re-activation" OR "re-tested positive" OR "reoccurrence" OR "re-occurrence" OR "post infection" OR "postinfection" OR "post-infection" OR "repositive" OR "re-tested positive")	723,902
#3	All=("whole genome sequencing" OR "seroconversion" OR "sero-conversion" OR "antibody response" OR "immune response" OR "viral strain" OR "viral clade" OR "variant")	539,469
#4	#1 AND #2 AND #3	**154**
MedLine		
#1	ti("covid-19") OR ti("covid19") OR ti("corona virus") OR	114,431

	ti("SARS-CoV-2") OR ti("Severe acute respiratory syndrome coronavirus 2") OR ti("2019nCoV") OR ti("2019 nCoV") OR ti("2019-nCoV") OR ti("HCoV-19") OR ti("coronavirus")	
#2	"Reinfection" OR "re-infection" OR "re-positive" OR "relapse" OR "repositive" OR "recurrence" OR "recurrent" OR "late presentation" OR "delayed presentation" OR "retested positive" OR "persistence" OR "Reactivation" OR "Re-activation" OR "re-tested positive" OR "reoccurrence" OR "re-occurrence" OR "post infection" OR "postinfection" OR "post-infection" OR "repositive" OR "re-tested positive"	1,809,586
#3	"whole genome sequencing" OR "seroconversion" OR "sero-conversion" OR "antibody response" OR "immune response" OR "viral strain" OR "viral clade" OR "variant"	1,049,617
#4	#1 AND #2 AND #3	**216**
	ti("covid-19" OR "covid19" OR "corona virus" OR "SARS-CoV-2" OR "Severe acute respiratory syndrome coronavirus 2" OR "2019nCoV" OR "2019 nCoV" OR "2019-nCoV" OR "HCoV-19" OR "coronavirus") AND ab("Reinfection" OR "re-infection" OR "re-positive" OR "relapse" OR "repositive" OR "recurrence" OR "recurrent" OR "late presentation" OR "delayed presentation" OR "retested positive" OR "persistence" OR "Reactivation" OR "Re-activation" OR "re-tested positive" OR "reoccurrence" OR "re-occurrence" OR "post infection" OR "postinfection" OR "post-infection" OR "repositive" OR "re-tested positive") AND ("whole genome sequencing" OR "seroconversion" OR "sero-conversion" OR "antibody response" OR "immune response" OR "viral strain" OR "viral clade" OR "variant")	
Oxford academic		
	(Title: covid-19 OR covid19 OR coronavirus OR corona virus OR SARS-CoV-2 OR Severe acute respiratory syndrome coronavirus 2 OR 2019nCoV OR 2019 nCoV OR 2019-nCoV OR HCoV-19) AND (Abstract: reinfection OR re-infection OR repositive OR re-positive OR relapse OR recurrence OR recurrent OR late presentation OR delayed presentation OR retested positive OR re-tested positive Or persistence OR reactivation OR re-activation OR retested-positive OR reoccurence OR re-occurence OR postinfection OR post-infection OR re-tested positive OR repositive) AND (whole genome sequencing OR seroconversion OR sero-conversion OR antibody response OR immune response OR viral strain OR viral clade OR variant)	**8**
Wiley		
	""covid-19" OR "covid19" OR "coronavirus" OR "corona virus" OR "SARS-CoV-2" OR "Severe acute respiratory	**93**

	syndrome coronavirus 2” OR “2019nCoV” OR “2019 nCoV” OR “2019-nCoV” OR “HCoV-19”"" in Title and ""Reinfection" OR "re-infection" OR "re-positive" OR "relapse" OR "repositive" OR "recurrence" OR "recurrent" OR "late presentation" OR "delayed presentation" OR "retested positive" OR "persistence" OR "Reactivation" OR "Re-activation" OR "re-tested positive" OR "reoccurrence" OR "re-occurrence" OR "post infection" OR "postinfection" OR "post-infection" OR "repositive" OR "re-tested positive"" in Abstract and ""whole genome sequencing" OR "seroconversion" OR "sero-conversion" OR "antibody response" OR "immune response" OR "viral strain" OR "viral clade" OR "variant”"" anywhere	
Cochrane library		
#1	("covid-19"):ti	4434
#2	("covid19"):ti	111
#3	("coronavirus"):ti	605
#4	("corona virus"):ti	63
#5	("SARS-CoV-2"):ti	60
#6	("severe acute respiratry syndrome coronavirus 2"):ti	0
#7	("2019nCoV"):ti	0
#8	("2019 nCoV"):ti	0
#9	("2019-nCoV"):ti	0
#10	("HCoV-19"):ti	0
#11	MeSH descriptor: [COVID-19] this term only	398
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	4930
#13	("reinfection"):ab	946
#14	("re-infection"):ab	300
#15	("repositive"):ab	0
#16	("re-positive"):ab	3
#17	("relapse"):ab	0
#18	("recurrence"):ab	31627
#19	("recurrent"):ab	27036
#20	("late presentation"):ab	60
#21	("delayed presentation"):ab	32
#22	("retested positive"):ab	2
#23	("re-tested positive"):ab	0
#24	("persistance"):ab	113
#25	("reactivation"):ab	1215
#26	("postinfection"):ab	69
#27	("post-infection"):ab	58
#28	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	77519
#29	("whole genome sequencing")	206
#30	("seroconversion")	3859
#31	("sero-conversion")	74
#32	("antibody response")	2805

#33	("immune response")	9593
#34	("viral strain")	24
#35	("viral clade")	0
#36	("viriant")	3743
#37	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	18300
#38	#12 AND #28 AND #37	**8**

Appendix B: Classification of severity levels according to WHO

Table A 2. COVID-19 Severity Classification According to WHO

Severity Classification	Manifestations
Mild disease	Symptomatic patients with no evidence of viral pneumonia or hypoxia
Moderate disease	Symptoms of pneumonia with no evidence of severe pneumonia and SpO2 ≥ 90% on room air
Severe disease	Symptoms of pneumonia with one of the following: respiratory rate more than 30 breaths per minute; severe respiratory distress; or SpO2 < 90% on room air
Critical disease	Acute respiratory distress syndrome (ARDS) [330-332] Sepsis [333, 334] Septic shock [333, 334] Acute thrombosis (Acute venous thromboembolism (i.e. pulmonary embolism, acute coronary syndrome, acute stroke.) Multisystemic inflammatory syndrome in children and adolescents (MIS-C) [335]

Appendix C: Quality assessment

Table A 3. Quality Assessment of Case Reports and Case Series Included Using the NIH Tool

First author	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well-described?	Were the results well-described?	Quality
Becky Mingyao	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
James P. Caralis	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Wu Jing	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Good
Christopher Chew	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Good
Line Heylen	Yes	No	N/A	N/A	N/A	Yes	Yes	N/A	Yes	Fair
Michael Mohseni	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Isabelo Sicsic Jr	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Belén Prado-Vivar	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Chengyun Dou	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Whilken Novoa	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Jessica Tuan	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Rohit Sharma	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Wei Chen	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Avani Jain	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Makoto Inada	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Satya Prakash Yadav	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Vivek Gupta	Yes	Yes	Yes	No	N/A	Yes	Yes	NR	Yes	Good
Jayanthi S Shastri	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair

Pauline Vetter	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
David Harrington	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Kelvin Kai-Wang To	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Resat Ozaras	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Kavita Gulati	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Bongiovanni, M.	Yes	No	Yes	No	N/A	Yes	Yes	NR	Yes	Fair
Satya Prakash Yadav	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Good
Mark I. Garvey	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Juliana D. Siqueira	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Helmut J. F. Salzer	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Philippe Colson	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Gabriela Sevillano	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Jee-Soo Lee	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Francesco Bellanti	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Lina Okrar	Yes	Yes	N/A	N/A	N/A	Yes	Yes	N/A	Yes	Fair
Bader Aldossary	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Natalia Fintelman-Rodrigues	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Fair
Richard L. Tillett	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Vagner Fonseca	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Nicole M Duggan	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Antonietta Coppola	Yes	Yes	N/A	N/A	N/A	Yes	Yes	N/A	Yes	Fair
Michelle Bentivegna	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Jian-Rong Yang et al.	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Anming Luo	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Sook Yin Loh	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Justin Wong	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Fair
Svenja Ravioli	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Shannon Leung	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Daniela Loconsole	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair

Chiara Vassallo	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Fábio de O. Martinez	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Saeed Shoar	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Richa Nepal	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Sameena Salcin	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Danielle de Araujo Torres	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Muhammad Hanif	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Hytham Fageeha	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Moayed Ibrahim	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Sully Marquez	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Fung Liu	Yes	Yes	N/A	N/A	N/A	Yes	Yes	N/A	Yes	Fair
Venkatraman Radhakrishnan	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Mariene R. Amorim	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Federica Novazzi	Yes	Yes	Yes	No	N/A	Yes	Yes	NR	Yes	Fair
J. Li,X.	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Mostafa Salehi-Vaziri	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Thomas Theo Brehm	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Kang Zhang	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Ana Carolina Fernandes	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Xiu-Feng Wan	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Philipp A. Reuken	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Noémie Zucman	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Good
Vijairam Selvaraj	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Serkan Atici	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Pallavali R. Rani	Yes	Yes	N/A	N/A	N/A	Yes	Yes	NR	Yes	Fair
Laith Abu-Raddad	Yes	Yes	Yes	Yes	N/A	Yes	Yes	NR	Yes	Fair
Na li	Yes	No	Yes	N/A	N/A	Yes	Yes	NR	Yes	Fair

Note: N/A: not applicable NR: not reported

Table A 4 Quality Assessment of Cohort Studies Included Using the Newcastle-Ottawa Scale Tool

	Selection				Comparability		Outcome		Quality
First Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Zhao, W		★	★	★			★		Fair
Tie-Jun Shui	★	★	★	★			★		Fair
Shengyang He	★	★	★	★	★		★		Fair
Lie Pan	★	N/A	★	★			★		Fair
Ji Zhou	★	★	★	★	★		★		Fair
Guangming Ye	★		★	★			★		Fair
Jie Chen	★	★	★	★			★		Fair
Yuan Liu	★	★	★	★	★		★		Fair
K. Fabiánová	★		★	★			★		Fair
Ithan D. Peltan	★	★	★	★			★		Good
J Zheng	★	★	★	★	★		★		Fair
Denggao Peng	★	★	★	★			★	★	Fair
Lu-Xiao	★	★	★	★			★		Fair
Victoria Jane Hall		★		★	★	★	★		Fair
Junjie Hu	★	★	★	★			★	★	Fair
Maolu Tian	★	N/A	★	★			★		Fair
Hua Yea		★	★	★			★		Fair
Chao Yang	★	★	★	★			★		Fair

Note: N/A= not applicable

Table A 5 Quality Assessment of Cross-sectional Studies Included Using the Newcastle-Ottawa Scale Tool

First author	Selection				Comparability	Outcome		Quality
	Representativeness of the exposed cohort	Sample size	Non-respondent	Ascertainment of the exposure (risk factor):	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.	Assessment of outcome	Statistical test:	
Jing Lu	★		★	★	N/A		★	Fair
Philippe Brouqui	★		★		N/A			Fair
Tao Liu	★		★		N/A		★	Fair
Aparna Mukherjee			★				★	Fair

Note: N/A= not applicable

Appendix D: STROBE checklist

Table A 6. Strobe Checklist

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	49
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	iii
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	49-52
Objectives	3	State specific objectives, including any prespecified hypotheses	52
Methods			
Study design	4	Present key elements of study design early in the paper	52
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	53
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	53
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	54-57
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	54-57
Bias	9	Describe any efforts to address potential sources of bias	58-59
Study size	10	Explain how the study size was arrived at	53
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	58-59
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	58-59
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	58
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	58-59
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	60
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	53
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	60-61
		(b) Indicate number of participants with missing data for each variable of interest	Presented in tables
Outcome data	15	Report numbers of outcome events or summary measures	61 68-69
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	64-65 73
		(*b*) Report category boundaries when continuous variables were categorized	54
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	75-77
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	83-84
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	77-80
Generalisability	21	Discuss the generalisability (external validity) of the study results	85
Other information			
Funding	22	Give the source of funding and the role of the	N/A

	funders for the present study and, if applicable, for the original study on which the present article is based

Note: N/A= not applicable

Appendix E: Directed acyclic graphs (DAGs)

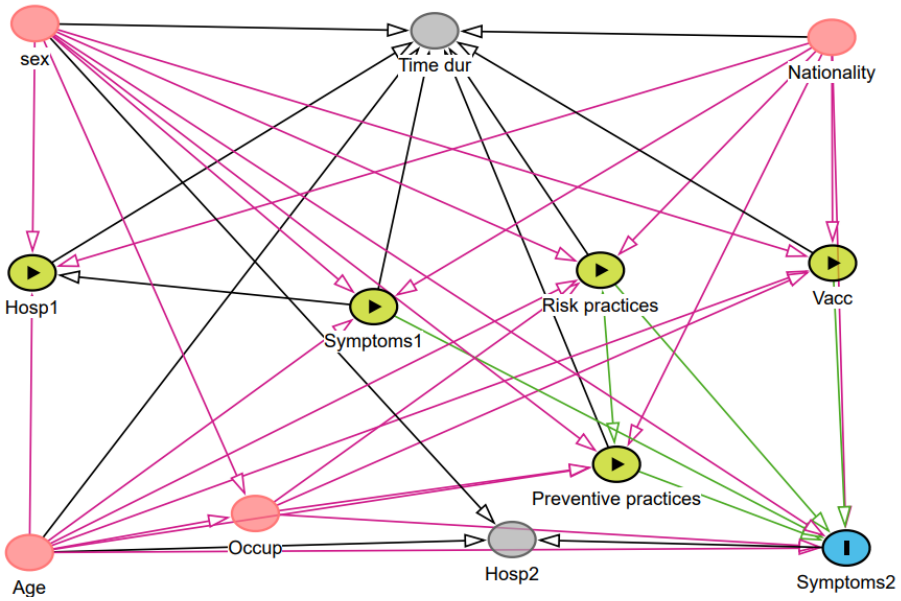

Figure A 1. Directed acyclic graph (DAG) model of symptomatic status of reinfection.

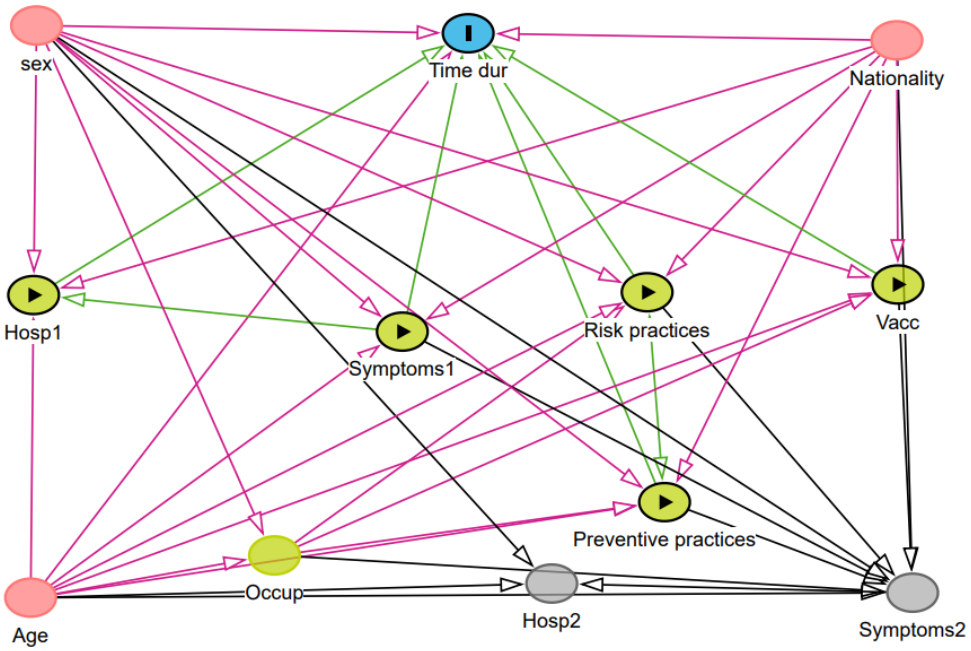

Figure A 2. Directed acyclic graph (DAG) model of time interval between two infections.

Appendix F: IRB Exempt Letters

Date: August 26, 2020

Ref. : ERC-826-3-2020

Exempt Research Certificate

Dear Applicant,

The Health Research Governance Department at the Ministry of Public health (MoPH) has reviewed the research project entitled "*COVID-19 Profile in the State of Qatar*". The Principal Investigator, Dr. Elmoubasher Abu Baker Abd Farag, confirmed that there will be no collection of identifiable information. Upon review, the research has been categorized as **exempt research under category (3):** Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified.

However, please note that in accordance with MoPH policy, the regulations state that "research involving…interview procedures…{**is exempt from this policy**} unless (1) information obtained is recorded in such a matter that human subject can be identified directly or through identifiers linked to the subject **and** (2) disclosure of the human subject responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation". Under conditions mentioned in (1) and (2), the proposal must be reviewed by an Institutional Review Board Committee.

If we can be of further assistance, please contact us at 974-4407-0363 or via email at IRB@moph.gov.qa

Sincerely,

Nardin Farhoush
on behalf of

Dr. Eman Sadoun
Manager, Research Division
Ministry of Public Health
E-mail: dresadoun@moph.gov.qa
Phone: 4407-0363

T: +974 44070000
P.O. Box: 42, Doha - Qatar
www.moph.qa

This information has been labeled as Public information

Figure A 3. IRB-MoPH exception letter.

Figure A 4. IRB-QU exception letter.

Qatar University Institutional Review Board **QU-IRB**

QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

DATE: October 18, 2021

TO: Manar Elhassan
FROM: Qatar University Institutional Review Board (QU-IRB)

PROJECT TITLE: 1812513-2 COVID-19 reinfection in Qatar
QU-IRB REFERENCE #: QU-IRB 1601-E/21
SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
REVIEW TYPE: Exempt Review
DECISION DATE: October 18, 2021

Approved Modifications:

- Change of the title "COVID-19 reinfection in Qatar", to change into "SARS-CoV-2 reinfection in Qatar".

Thank you for your submission of Amendment/Modification materials for this project. The Qatar University Institutional Review Board (QU-IRB) has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a project design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Exempt Review according to Qatar Ministry of Public Health (MoPH) regulations.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Qatar MoPH regulations require that each participant receives a copy of the consent document.

Please note that exempted proposals do not require renewals however, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation. In addition, please submit a closure report to QU-IRB upon the completion of this project.

All UNANTICIPATED PROBLEMS involving risks to subjects or others (UPIRSOs) and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

Please note that all research records must be retained for a minimum of three years after the completion of the project.

Documents Reviewed:

- Amendment/Modification - QU-IRB Brief Application-SARS-CoV-2 reinfection.pdf (UPLOADED: 10/7/2021)
- Amendment/Modification - QU-IRB Renewal-Modf. SARS-CoV-2 reinfection.pdf (UPLOADED: 10/7/2021)

- Other - Reviewed & Approved Documents.pdf (UPLOADED: 10/6/2021)
- Other - IRBNetDocument.pdf (UPLOADED: 10/6/2021)

If you have any questions, please contact QU-IRB at 4403 5307 or qu-irb@qu.edu.qa. Please include your project title and reference number in all correspondence with this committee.

Best wishes,

Dr. Mohamed Emara
Chairperson, QU-IRB

Institutional Review Board (IRB) Office Of Academic Research

This letter has been issued in accordance with all applicable regulations, and a copy is retained within Qatar University's records.

Qatar University-Institutional Review Board (QU-IRB), P.O. Box 2713 Doha, Qatar
Tel +974 4403-5307 (GMT +3hrs) email: QU-IRB@qu.edu.qa

Appendix G: Table of characteristics of reinfected cases

Table A 7. Characteristics of Reinfected Cases After at Least 90 Days

	Time interval ≥90 days N=411
Age in years*	33.88±10.73
Age categorized	
≤20	26 (6.3%)
21-40	294 (71.5%)
41-60	86 (20.9%)
>60	5 (1.2%)
Missing	0 (0.0%)
Gender	
Female	64 (15.6%)
Male	347 (84.4%)
Missing	0 (0.0%)
Nationality	
Other	11 (2.7%)
Arab	89 (21.7%)
Asian	311 (75.7%)
Occupation	
Blue Collar Workers	236 (57.4%)
White Collar Workers	66 (16.1%)
Healthcare Workers	19 (4.6%)
Admin	23 (5.6%)
Army and police	21 (5.1%)
Students and children	20 (4.9%)
Unemployed, Retired and Housewives	26 (6.3%)
Symptomatic status of first infection	
No	165 (40.1%)
Yes	242 (58.9%)
Missing	4 (1.0%)
Symptomatic status reinfection	
No	249 (60.6%)
Yes	161 (39.2%)
Missing	1 (0.2%)
Hospitalization status of first infection	
No	368 (89.5%)
Yes	37 (9.0%)
Missing	6 (1.5%)
Hospitalization status of reinfection	
No	389 (94.6%)
Yes	14 (3.4%)
Missing	8 (1.9%)
Vaccination status before reinfection	
No	381 (92.7%)
Yes, fully vaccinated	15 (3.6%)
Yes, first dose	15 (3.6%)
Missing	-
Time interval between the first and second infections in days**	309 (275-333)
Reason for testing first infection	
Clinical suspicion	124 (30.2%)

	Time interval ≥90 days N=411
Contact of a case	148 (36.0%)
Routine surveillance	102 (24.8%)
Port of entry	33 (8.0%)
Missing	4 (1.0%)
Reason for testing reinfection	
Clinical suspicion	152 (37.0%)
Contact of a case	35 (8.5%)
Routine surveillance	129 (31.4%)
Port of entry	95 (23.1%)
Wearing Mask after first Infection	
Never	3 (0.7%)
Sometimes	29 (7.1%)
Always	374 (91.0%)
Missing	5 (1.2%)
Keeping social distance after first Infection	
Never	11 (2.7%)
Sometimes	55 (13.4%)
Always	340 (82.7%)
Missing	5 (1.2%)
Hand hygiene after first Infection	
Never	4 (1.0%)
Sometimes	50 (12.2%)
Always	352 (85.6%)
Missing	5 (1.2%)
Physical contact after first Infection	
Never	300 (73.0%)
Sometimes	75 (18.2%)
Always	30 (7.3%)
Missing	6 (1.5%)
Social Gathering after first Infection	
Never	293 (71.3%)
Sometimes	101 (24.6%)
Always	12 (2.9%)
Missing	5 (1.2%)
Combined preventive practices	
Sometimes[+]	92 (22.4%)
Always [++]	314 (76.4%)
Missing	5 (1.2%)
Combined risk practices	
Never[+++]	247 (60.1%)
Sometimes or always[++++]	158 (38.4%)
Missing	6 (1.5%)

Note: Data are presented as n (%) for categorical measures.

[*] Presented as mean ±SD [**] Presented as Median (IQR)

[+]sometimes perform some of the preventive practices [++]Always perform all preventive practices [+++]Never engage in any risk practice [++++]sometimes engage in some risk practices or always engage in all risk practices