

Current Control Measures for SARS-CoV-2 the Aetiological Agent of COVID-19

Elaine Meade¹, Micheal Savage² and Mary Garvey^{1,2}

¹Department of Life Science, Institute of Technology, Sligo, Ash Lane, Sligo, Ireland.

²Lir Analytical LTD, Athlone Rd, Longford, Ireland.

*Correspondence:

Dr Mary Garvey, Dept. of Life Science, Institute of Technology Sligo, Ash Lane, Sligo, Ireland, Tel: 071 9305529.

Received: 23 October 2021; Accepted: 29 November 2021

Citation: Meade E, Savage M, Garvey M. Current Control Measures for SARS-CoV-2 the Aetiological Agent of COVID-19. *Microbiol Infect Dis.* 2021; 5(6): 1-9.

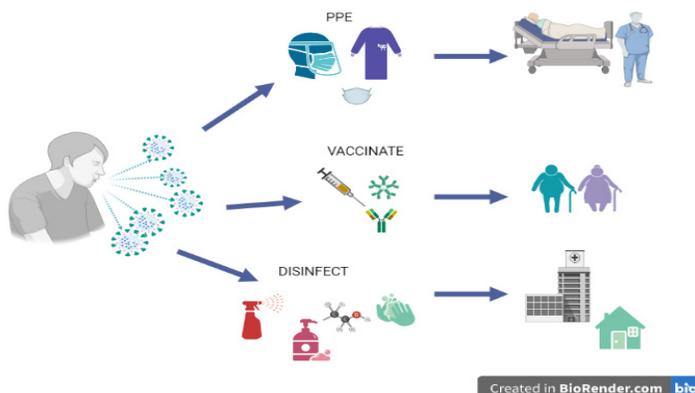
ABSTRACT

Severe acute respiratory syndrome coronavirus 2, the aetiological agent of COVID-19 continues to be a threat to public health globally. Viral transmission is horizontal from person-to-person via cough, sneeze and droplets with surface spreading also possible. Disease can progress to severe or life-threatening requiring hospitalisation and oxygen therapy with acute respiratory distress syndrome and multiple organ failure often evident. While non-therapeutic controls measure such as restricting the movement of people and recurrent lockdowns have proven vital to preventing disease transmission, such action has had substantial impact on economies across the globe with a global recession to be expected. Disease prevention measures implemented to curtail the pandemic is heavily reliant on effective biocide control measures with the EPA listing suitable viricidal disinfectants for use. The unprecedented demand for PPE has led to supply shortages with efforts to establish suitable sterilisation methods for re-purposing PPE materials. As variants of concern emerge globally, concern has arisen relating to the efficacy of current vaccination programmes to protect against each new strain displaying increased transmissibility. This review discusses the epidemiology of COVID-19 highlighting viral virulence factors promoting pathogenicity and current control measures therapeutic and non-therapeutic in use as best practice preventative measures.

Keywords

SARS-CoV-2, COVID-19, Virulence, Pathogenicity, Disease management.

Graphical Abstract



Introduction

SARS-CoV-2 a newly emerged Coronavirus is the aetiological agent of COVID-19, where humans have proven immune deficient with certain cohorts highly susceptible to disease and mortality. The first case of COVID-19 occurred in Wuhan China in December 2019 and spread globally in early 2020 with the World Health Organization (WHO) announcing an international Public Health Emergency on January 30th, 2020 and pandemic in March of that year [1]. Coronaviruses (CoVs) are large, pleomorphic, enveloped RNA viruses belonging to the family Coronaviridae. CoVs are known to infect mammals and birds with viruses first identified in human respiratory and enteric cases of disease in the 1960s [2]. Seven CoVs strains are known to infect humans with three emerging in the last 20 years as severe respiratory pathogens including severe acute respiratory syndrome coronavirus 1 or SARS-CoV-1 (SARS), the Middle-East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the

causative agent of COVID-19, where the remaining four (229E, NL63, OC43, and HKU1) cause common cold symptoms. SARS-CoV-2, SARS-CoV, and MERS-CoV have a mortality rate of 2%, 9.6%, and 35.5% respectively [3] with SARS-CoV-2 being more transmissible. The increase likelihood of transmission of SARS-CoV-2 may relate to its location in the upper respiratory tract of patients with droplet and aerosol transmission occurring where SARS and MERS have tropism for lower respiratory airways [4]. Coronaviruses frequently shift hosts moving from animals to humans termed zoonosis, resulting in new animal and human diseases where SARS-CoV-2 is believed to have transmitted to humans from bats via an intermediary host reservoir. As zoonotic species SARS, MERS and COVID-19 highlight the importance of viruses as emerging and re-emerging pathogens capable of global impact with dire health and socio-economic consequences. Due to the innate ability of viral species to mutate and generate variants with unknown pathogenicity, preventing viral transmission remains essential. With limited treatment options and slow vaccine role out in some regions, preventing SARS-CoV-2 transmission remains critical to control disease spread. Prolonged, widespread “lockdowns” have become the mainstay since March 2020, globally. The substantial costs of overburdened medical systems, loss of income, closure of business, retail, education sectors, hospitality, tourism, and aviation has substantially impacted economies at a global scale. This concurrent economic shutdown may initiate a prolonged global recession, having severe and unparalleled financial impact globally [5]. Furthermore, persistent lockdown and social distancing measures have amplified anxiety, depression, domestic violence (physical, emotional, sexual) [6] an important externality of the ongoing pandemic. This review outlines key factors relating to SARS-CoV-2 virulence and pathogenicity in terms of the triad of disease. The author informs on best practices essential to decrease disease prevalence and reduce the impact of COVID-19.

SARS-CoV-2 pathogenicity – the triad of disease

The epidemiological triad of disease is a tool implemented to determine the spread of infectious disease. In the context of COVID-19 the agent is SARS-CoV-2, the host is the human patient and/or carrier and the environment relates to external factors enabling disease transmission. A clear understanding of the triad of COVID-19 will allow for enhanced control measures (figure 1) and reduced disease transmission particularly amongst highly susceptible persons in environments such as hospitals and elderly care centres where outbreaks are prominent. While associated with less fatality, studies have demonstrated that SARS-CoV-2 is significantly more transmissible between humans than SARS and MERS [7], having a higher reproduction number (R₀). SARS-CoV-2 has an R₀ estimate between 2.2 and 3.9 and region dependent mortality estimate of between 0.8% and 14.5% [8]. The pathogenicity of SARS-CoV-2 relates to viral virulence factors enabling it to evade host immunity and survive in the host environment until horizontal transmission occurs, increasing case numbers. According to the WHO a case of COVID-19 is a person with laboratory confirmation of SARS-CoV-2 (detection of viral RNA via PCR) without necessitating clinical signs of disease [9].

The virus

SARS-CoV-2, SARS-CoV and MERS belong to the genus of betacoronaviruses, of the family Coronaviridae. Coronaviruses have genetic diversity due to their large RNA genome, genetic variation, genetic flexibility, RNA error prone polymerase and homologous recombination creating selective pressure for viral replication [10]. SARS-CoV-2 has genome of approximately 30 kB encoding 9860 amino acids and shares 79% gene sequence identity with SARS-CoV, and approximately 50% identity with MERS-CoV [2]. SARS-CoV-2 has four major structural proteins namely the spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and numerous accessory proteins [11]. The spike glycoprotein a transmembrane protein, is the key to host-cell entry via host receptors namely angiotensin-converting enzyme 2 (ACE2) on type II alveolar cells of the respiratory tract inducing pneumonia leading to Acute Respiratory Distress Syndrome (ARDS). ACE2 receptors are also present on cells of the upper oesophagus, stratified epithelial cells, cells of the ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells causing secondary conditions of the heart, kidneys, and digestive tract [12]. Viral spikes have a polysaccharide coat as a camouflage mechanism evading host immunity [13]. The E glycoprotein a 75 amino acid long protein (both monomeric and homo-pentameric forms) is associated with intracellular transportation, viral assembly, viral maturation and infection and is highly immunogenic [14]. While the M protein is associated with the envelope shape and the nucleocapsid (N) protein is essential for the synthesis of RNA and is the structural protein of the virus [15]. The N protein also packs the RNA into a protective helical ribonucleocapsid (RNP). The viral mRNA is released and translated in protein with 14 open reading frames (ORF) encoding a variety of structural and non-structural proteins essential for survival and pathogenicity. The mRNA is translated by host ribosomes which generates SARS-CoV-2 viral replicative enzymes essential for new RNA genomes and the synthesis of new viral particles [16]. Viral virulence is also achieved via suppression of host gene expression and blocking innate immune responses due to the activity of non-structural protein 1 (Nsp1) [17]. Genetic mutations are key to viral adaptability and survival with new emerging viruses gaining the ability to jump host species due to genetic diversity, error-prone replication and frequent recombination's [18]. Selective pressure from host immunity induces survival adaptive strategies in viruses where RNA viruses have a greater mutation rate than DNA viruses. The genetic diversity of SARS-coV-2 is low however, due to Coronavirus genetic proof-reading mechanisms [8] possibly due to the activity of non-structural protein 14 (nsp14). Antigenic drift the slow accumulation of gene mutations and antigenic shift where one major genetic change occurs are drivers for viral evolution and the emergence of species variants. With prolonged host exposure and interaction with complex immunological mechanisms as seen in pandemic situations the occurrence of antigenic drift in SARS-CoV-2 becomes increasingly possible. As such it is imperative to

monitor the virus in animal and human reservoirs [19]. Mutations coding for alterations of the D614G, H69 and V70 amino acids in the receptor binding domain of SARS-CoV-2 spike protein [20] is associated with increased infectivity and the emergence of variants of concern (VOC). Where such variants have become the dominant strains of the COVID-19 pandemic [8]. The European CDC reports on SARS-Cov-2 variants of concern namely B.1.1.7 (Alpha) and B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) that exhibit greater transmissibility and immune evasion than the wildtype strain with an increased risk of hospitalization and mortality [21]. The Infective dose (ID), the dose of viral particles required to initiate disease in a host, of SARS-CoV-2 or its VOCs have not been elucidated. Importantly, elucidating the possibility of a dose response relationship between viral load and disease severity may inform on the immune response seen in mild or severe cases of COVID-19 [22].

The host

Similar to SARS and MERS, the symptoms of COVID-19 include malaise, lethargy, dry cough, upper chest irritation, irregular diarrhoea, and hyperventilation. Issues relating to a loss of smell and/or taste are also recognized as common symptoms of COVID-19. In severe cases secondary infections, sepsis and multi

organ failure is evident with hospitalised patients manifesting with pneumonia, lymphopenia, and pulmonary dysfunction [23]. Additional factors such as age and co-morbidities (cancer, chronic kidney, heart, liver and lung disease, obesity, immunosuppression) are associated with severe COVID-19 and acute respiratory distress syndrome, organ failure and mortality [24]. Interestingly, epidemiology studies indicate that blood type and Rhesus factor (Rh) play an inheritable role in SARS-CoV-2 disease severity with blood group A being higher risk than O and Rh+ higher risk than Rh- [25]. The success and pathogenicity of infectious agents including SARS-CoV-2 relies on their ability to undermine the host immune response. The host immune system (innate and acquired/adaptive) is responsible for eradicating infectious invaders and maintaining health. Following viral exposure, innate defences are triggered via pathogen recognition receptors (PRRs) e.g., toll-like receptors (TLRs) on plasma and endosomal membranes and retinoic acid-inducible gene I like receptors (RLRs) in the cytosol which recognise pathogen-associated molecular patterns (PAMPs). Innate immunity attempts to block or inhibit infection or eliminate infected cells via activation of these PRRs [26] and a subsequent immune cascade. Coronavirus, however, can evade PRR activation by replicating in the membrane of the endoplasmic reticulum which is devoid of PRRs reducing viral contact to RLRs

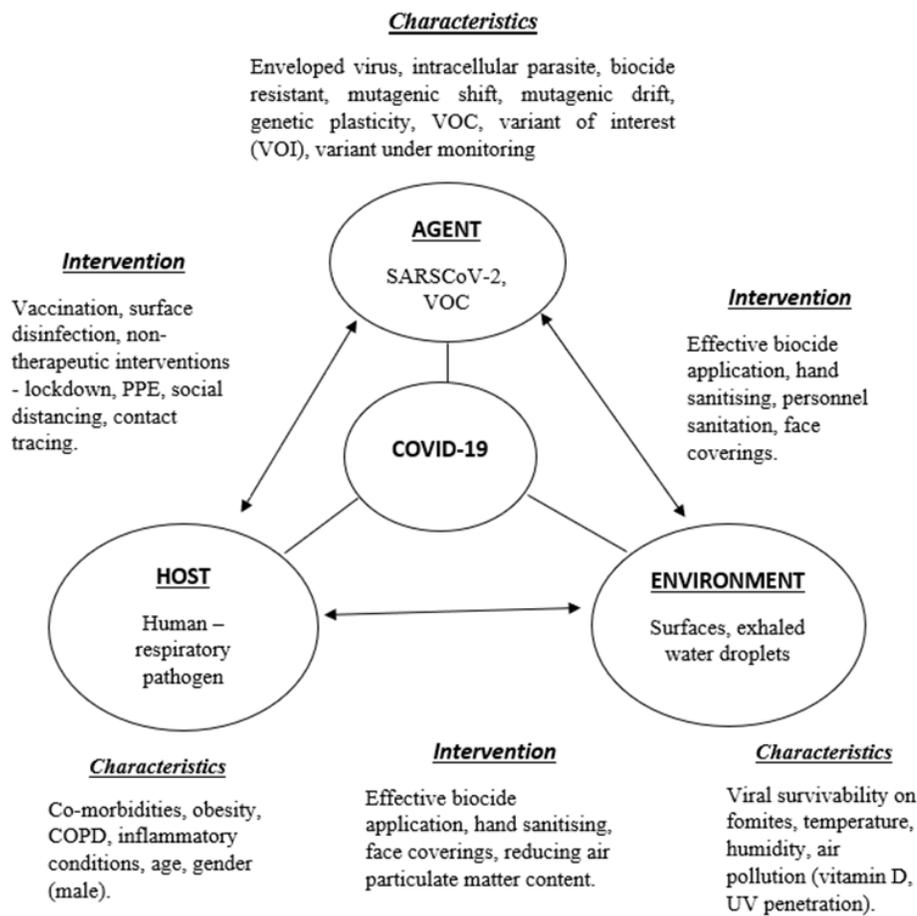


Figure 1: The triad of COVID-19 outlining associated characteristics promoting virulence and intervention methods to reduce disease transmission.

and TLRs [23] a technique also likely observed in SARS-CoV-2. Viruses provoke key host responses including the induction and maturation of dendritic cells, macrophages, lymphocytes and parenchymal cells and the release of interferons (IFN) and cytokines [27]. IFN-1 in particular is vital for viral clearance, SARS-CoV-2 like many viruses, however, can inhibit IFN production with early-stage Covid-19 patients having a limited INF-1 response and signalling [28]. IFN-1 activates natural killer (NK) cells which can kill host infected cells and stimulates proinflammatory cytokine release including interleukins (ILs). SARS-CoV-2 has tropism for the upper respiratory tract where infection, replication and transmission occur. Type I and III IF play a vital role in limiting viral replication and localisation to the lower respiratory tract where damage to alveolar tissues can impact gaseous exchange [29]. Cytokines TNF- α , IL-12, and IL-6 activate TLR-7 which promotes the generation of specific cytotoxic CD8+ T cells which stimulate B cells to produce viral antibodies, immunoglobulins namely IgG and IgM [24]. SARS-CoV-2 can block T cell function by inducing T cell apoptosis allowing virally infected cells to escape destruction enabling viral replication to completion. Noteworthy, persistent lymphopenia in Covid-19 patients affecting helper T cells (CD4+ and CD8+ T cells) B cells and NK cells is associated with severe disease and mortality in older patients [30]. IL-6 is one of the most essential cytokines in viral infection as it regulates T-cell response, inflammatory resolution, macrophage activity and regulation of IgG where high serum levels of IL-6 in Covid-19 patients is associated with cytokine storm and a high risk of respiratory failure [31]. Over production of proinflammatory cytokines drives the cytokine storm and is related to oedema, respiratory dysfunction, acute respiratory and cardiac injury, and secondary infection in Covid-19 patients [24] while simultaneously failing to mount an adequate anti-viral interferon response [23]. SARS-CoV-2 can also infect host macrophages thus evading immune responses and allowing it to migrate to the spleen and lymph nodes while triggering the release of IL-6 and TNF- α [32] further promoting tissue damage and lymphopenia. SARS-CoV-2 can also infect dendritic cells preventing maturation and reducing the activation of T cells decreasing the efficiency of the adaptive immune response and potentially impacting long term humoral immunity in the patient [33].

The environment (Transmission)

The major transmission routes of SARS-CoV-2 which occurs during the viral incubation period of 2–10 days is via direct contact, droplet transmission, airborne transmission with indirect fomite transmission also a possibility [34]. The CDC states however, that the proportion of COVID-19 cases attributed to surface/fomite transmission is unknown as multiple transmission routes are often present with confirming fomites as environmental sources difficult due to the presence of asymptomatic viral carriers [35]. The faecal-oral route, wastewater and sewage as modes of transmission remain worthy of investigation but have not been directly linked to disease outbreak [34]. Transmission via respiratory droplets emitted via talking, sneezing and coughing is therefore, the dominant mode, where heterogeneous

transmission causes clusters of disease outbreak, where some infected persons fail to transmit the virus while others cause transmission clusters termed superspreading events [36]. Droplets can range from $<1 \mu\text{m}$ to $>100 \mu\text{m}$ in diameter and can remain suspended in air being considered airborne droplets, with factors such as air flow, humidity and temperature affecting their spread [37]. Droplet size and spread is an important consideration in social distancing where 1-2 metres is considered the safe distance reducing transmission. Droplets of 50–100 μm however, can be carried further than 2 metres in an expulsion of air as with sneezing or coughing [37]. Aerosol transmission during regular communication (speech) in indoor settings, however, may offer insight into transmission by asymptomatic and pre-symptomatic persons who are not manifesting with respiratory symptoms such as coughing [34]. Interestingly, approximately 40,000 droplets per sneeze, 710 particles per cough, and 36 particles per 100 words spoken are discharged [9]. Environmental factors such as weather, humidity, temperature, air pollution also impact transmission rates [38]. Assessing the impact of air pollution on SARS-CoV-2 transmission is problematic as control strategies such as global lockdowns have reduced anthropogenic atmospheric pollution. Additionally, while residing in highly polluted cities may affect susceptibility to severe infections due to cardiopulmonary and metabolic diseases it is currently unknown however, if polluted air may increase transmission of the virus. Particulate matter in air however can reduce the virucidal activity of UV light by inhibiting UV penetration and reduce vitamin D synthesis in persons potentially increasing disease severity [39]. The survivability and transmissibility of SARS-CoV-2 on surfaces is an area of ongoing investigation. Viable viruses have been detected on porous surfaces hours after contact and weeks post contact on non-porous surfaces such as stainless steel, plastic and glass [35] however, the transmissibility and infectivity of such viruses remains unclear. Importantly, coronaviruses have lower persistence times (<2 days) on disposable materials including latex gloves, cotton gowns and gauze sponges [40]. Nosocomial transmission of SARS-CoV-2 remains a key contributor to incidence of disease where health care settings and elderly homes are hotspots of infection. Studies assessing the presence of viral genes on hospital surfaces 28 days post discharge report the presence of gene fragments via real time PCR [33]. While the likelihood of infectivity from viral gene segments is unknown, it is unlikely however, as gaining entry to host lung cells requires binding to host cell receptors by means of the viral spike protein. Transmission in clinical settings is affected by factors such as population density, age, gender, immune and health status of residents, and climate conditions in situ such as temperature and humidity. The effect of seasonality on SARS-CoV-2 transmission is not fully elucidated as factors such as socio-economic circumstances, implementation of non-pharmaceutical control measures and hemisphere location impact on disease prevalence, where missing the environmental impacts of Covid-19 will limit disease management [41]. The seasonality of COVID-19 is an important consideration, as it will inform on the likelihood of a 4th and subsequent waves of disease outbreak [42].

Control measures mitigating the impact of COVID-19

Preventative measures remain the most effective approach to mitigating the impact of COVID-19 and reducing the burden on healthcare systems globally. Non-therapeutic prevention measures including lock downs, quarantine, social distancing, face coverings, regular hand sanitising, testing and contact tracing is enforced to reduce viral transmission [43]. Additionally, international health agencies outline effective cleaning and disinfection strategies which should be implemented domestically, as sanitisers and in healthcare facilities [9]. In the absence of sufficient vaccine quantities and effective drug therapy, disinfection and other non-therapeutic methods play a vital role in preventing and controlling the spread of COVID-19.

Biocides/disinfectants and Personal Protective Equipment

The Environmental Protection Agency (EPA) outlines a list termed List N of registered disinfectants and combinations suitable for use against SARS-CoV-2 including hydrogen peroxide (H₂O₂), phenolic, quaternary ammonium compounds (QACs), ethanol, isopropanol (IPA), chloride dioxide and sodium hypochlorite amongst others (Table 1). As with all microbes, the efficacy of biocides against viruses depends on many factors including mode of action, concentration, contact time, presence of inhibitors and innate resistance of the organism. Enveloped viruses including SARS-CoV-2 are considered more susceptible to chemical inactivation than non-enveloped species due to the envelope lipid matrix. Following exposure, viral inactivation is due to destruction of the lipid envelope, protein denaturation and coagulation, and alteration of genetic material via nucleic acid denaturation [44]. According to EPA guidelines, biocide manufacturers must supply data demonstrating potential efficacy against hard to inactivate viruses in order to market claims as active against SARS-CoV-2 [45]. The European Standard test EN 14476 for demonstrating virucidal efficacy requires a 4-log reduction in viral load of surrogate enveloped species where the framework of the European Committee for Standardisation (CEN) names vaccinia as a

surrogate for SARS-CoV-2 [46]. As a biosafety level 3 pathogen, determining the efficacy of biocides is difficult where surrogate species such as human coronavirus HCoV-229E also serve as indicators of inactivation using cell line infectivity and the tissue culture infectious dose (TCID) [47], viral plaque assays or PCR methods. Variations in experimental procedures such as contact time, concentration, chemical combinations, viral load, and a lack of standardised methods also influence the comparability of inactivation data generated. For surface disinfection repeated cleaning to remove interfering substances and disinfection is required for reducing viral load. Commercial disinfectants demonstrating efficacy against SARS-CoV-2 (4 log reduction) include 0.1% benzalkonium chloride (BAC), 30–80% ethanol, 30–75% propanol, 0.45–7.5% povidone-iodine and 5–6% sodium hypochlorite [40]. H₂O₂ is typically effective against enveloped viruses, coronaviruses appear more resistant however with a moderate 1–1.8 log reduction at 6% with 30 seconds exposure [48] where viral load in clinical settings have been detected at < 5.2 log in intensive care units and <4 log in general wards [49]. For hand sanitisers the WHO recommends the use of 75% IPA or 80% ethanol with 30 seconds contact time [9]. 2 categories of hands sanitisers exist; alcohol based containing ethanol or IPA and non-alcohol based commonly containing QAC compounds [50] including humectants and excipients. QACs have proven effective at inactivating SARS-CoV-2 including a BAC based hand sanitizer in short contact times [51]. For SARS-CoV-2, thermal inactivation has proven quite effective at 56°C for 30 minutes, 95°C for 10 minutes and 98°C for 2 minutes providing 5 log₁₀ inactivation [52]. This is beneficial for the sterilisation of non-heat sensitive personal protective equipment (PPE) products and face masks including homemade masks (non-surgical) which are part of the non-therapeutic preventative measures. Studies have demonstrated the efficacy of surgical and non-surgical masks to reduce the inhalation of particles by the wearer, with surgical masks preventing viral dissemination by infected persons up to 100% [37]. PPE including gowns, face masks, face shields, and N-95 facepiece respirators

Table 1: Outlining chemical disinfectants used to control SARS-CoV-19, their mode of action and disinfection parameters.

Disinfectant	Mode of action	Parameters	Comments
Oxidising agents (H ₂ O ₂ , peracetic acid, ozone)	Oxidation of cell envelope, free radicals disrupt essential biomolecules	0.5% for 1 minute	Inhibited by organic matter, degrade rapidly, environmentally friendly.
Phenol-based disinfectants mixed with IPA or ethanol	Protein destabilisation, membrane damage	200 ppm phenol with varied concentrations of IPA, 10 minutes hard non-porous surfaces	Most effective at acidic pH, Kills a harder-to-kill pathogen than SARS-CoV-2, phenol is toxic and carcinogenic.
Chlorine-releasing agents (sodium hypochlorite)	Nucleic acid disruption, membrane damage	0.1% for 1 minute	Environmental pollutant, most effective at acidic pH
QACs	Membrane damage	0.04% w/v, 1 min, steel surfaces	Promotes antibiotic resistance, QAC resistance evident, environmental pollutant, are most potent at alkaline pH
Formaldehyde and glutaraldehyde	Chemically alkylating proteins and nucleic acid bases	glutaraldehyde (0.5–2.5%), formaldehyde (0.7–1%) for 2 minutes	High level disinfectants, environmental pollution
Iodine-releasing agents (povidone-iodine)	Nucleic acid disruption, membrane damage, protein destabilisation	0.2% for rapid skin, oral cavity, and nasal disinfection. 7.5 to 10% skin disinfection, clinical use in antiseptic hand washes	Toxic, excessive use can be corrosive, eye irritation, may cause thyroid issues
Alcohols (ethanol, IPA)	membrane damage, disrupt cell envelope, protein denaturation, RNA damage	70–90%, 30 secs	Slow acting and evaporate easily, no residual germicidal effect, poor penetration organic material, not useful for sterilisation

Table 2: Current therapeutics used in the treatment of COVID-19.

Therapeutic	Drug type	Recommended use*	Comments
Remdesivir	Anti-viral	hospitalized patients needing O ₂	Potential for hepatic and renal adverse events (Scavone et al., 2020)
Dexamethasone	Corticosteroid	hospitalized patients needing O ₂ and ventilation	Immune modulator - inhibit the action and expression of molecules involved in pneumonia associated inflammatory response (Patel et al., 2020)
Tocilizumab	Monoclonal antibody	jointly with dexamethasone therapy for respiratory decompensation	Reduce the impact of cytokine storm in severe cases of disease. Side effects include infections, headache, hypertension (Scavone et al., 2020), can cause autoimmune diseases and damage body tissues (Samaee et al., 2020).
Bamlanivimab and Etesevimab Casirivimab and Imdevimab	Monoclonal antibodies	mild to moderate disease with chance of progression	Neutralising the receptor binding domain of S protein (Taylor et al., 2021)

*Recommended by the National Institutes of Health

(FFR) are essential to prevent the clinical transmission of SARS-CoV-2 and to protect essential health care staff. Reusable medical textiles can be effectively sterilised with dry steam with the CDC recommending EPA registered disinfectants for sterilizing face shields and goggles [53]. The sterility assurance level (SAL) for the sterilisation of medical PPE requires a 6-log reduction in viability as outlined by the FDA. Ultraviolet light (UV) namely UVC has virucidal activity when applied to surfaces, penetration however is an issue making it unreliable for some PPE. Ionizing radiation such as gamma rays, however, have better penetration but can negatively impact the material where studies show gamma treatment modified the electrostatic charge on respirator filters decreasing the filtering capacity of the respirator [54]. Vaporized H₂O₂ (30 to 35%), moist heat (60 to 65°C for 30 min) and UV light at 254 nm has been utilized for sterilising medical masks and N95 respirators for re-use [55] to combat PPE shortage. Vaporised H₂O₂ has been authorized under emergency use authorization (EUA) for the sterilisation of N95 face masks for re-use by the USFDA [56].

Therapeutics

The therapeutic approaches for COVID-19 rely on the use of antivirals preventing viral replication (early stage of clinical disease) and immune modulators regulating the host immune response (later stage of clinical disease) coupled with supportive oxygen therapy. As the immune response becomes dysregulated (cytokine storm) in later stages of disease leading to tissue damage, the use of immune modulators is often warranted. Failing to treat the cytokine/inflammatory storm can promote progression from acute respiratory distress syndrome, multiorgan dysfunction, and mortality [57]. Remdesivir is the only antiviral drug currently approved by the FDA for COVID-19 and is recommended for patients requiring oxygen treatment where other antiviral drugs are administered off label [58]. Studies show that remdesivir shortened recovery time in hospitalised COVID-19 patients where the lower respiratory tract appeared infected [59]. Side effects of remdesivir include diarrhoea, nausea, hypotension, liver and kidney damage with serious effects observed in 23% of patients [60]. In mild to moderate cases of COVID-19 which are not considered a high risk for disease progression, therapy is not considered beneficial where management of symptoms and preventing viral transmission are considered important. For patients who are a high risk of disease progression monoclonal antibodies (Mab) are administered as therapy in the early stages of disease (Table 2). In February

2021, the FDA issued an EUA for the use of the neutralising Mabs Bamlanivimab and Etesevimab jointly for the treatment of mild to moderate COVID-19 in patients over 12 years who are not hospitalised or requiring oxygen where disease progression is high risk [61]. A combination of Casirivimab and Imdevimab is also used for the treatment of non-hospitalized patients with mild-to-moderate disease. These Mabs target the receptor binding domain of the S protein of SARS-CoV-2 which is required for entry into host cells via receptor binding. Neutralising the receptor binding domain prevents host cell entry [62] reducing cellular infectivity. The Mab tocilizumab is an anti-IL-6 receptor monoclonal antibody that inhibits IL-6 signalling thus reducing over inflammatory reactions as seen in the inflammatory storm. At present, retrospective studies aiming to determine tocilizumab efficacy in COVID-19 patients are contradictory with a lack of evidence-based studies emerging [63]. Studies report however, that blockage of IL-6 does not hinder the SARS-CoV-2 antibody response but may reduce the risk of death among severely ill COVID-19 patients [60]. In September 2020, the WHO issued a guide document on the use of corticosteroids for the treatment of COVID-19 based on the findings of clinical trials. The use of oral or IV corticosteroids including dexamethasone, hydrocortisone or prednisone in severe and critical patients is recommended for 7 to 10 days [64]. Dexamethasone reduces mortality in hospitalised patients on oxygen support by 20% and mechanical ventilation by 35% with no benefits observed in mild, moderate or non-oxygenated hospital patients [65]. The FDA has established the special emergency program to establish the safety and efficacy of possible Coronavirus therapeutics termed the Coronavirus Treatment Acceleration Program (CTAP) where numerous studies and clinical trials are investigating various pharmacological options for the treatment of COVID-19 [60].

Vaccination

Currently there are 4 COVID-19 vaccines authorised for use in the European Union, Comirnaty, COVID-19 Vaccine Moderna, Vaxzevria (AstraZeneca) and COVID-19 Vaccine Janssen [66]. The USFDA issued an EUA allowing the use of the mRNA Pfizer-BioNTech COVID-19 Vaccine (BNT162b2 vaccine) to be distributed in the U.S in December 2020 with Vaccine Modern and Janssen also being implemented. Comirnaty, BNT162b2 and Moderna are mRNA vaccines containing mRNA coding for the spike protein where Vaxzevria and Vaccine Janssen utilise a

modified adenovirus containing a gene coding for SARS-CoV-2 spike protein, the immunogenic element of the virus. Upon replication using host cell ribosomes, the spike protein should trigger an immune response creating SARS-CoV-2 antibodies. The EMA also has a rolling review in place for CVnCoV, NVX-CoV2373, COVID-19 Vaccine (Vero Cell) Inactivated and Sputnik (Gam-COVID-Vac) vaccines since February 2021. Randomized clinical trials demonstrate an efficacy of 94 to 95% for mRNA-based vaccines for preventing Covid-19 [67]. It is important to note however, that the efficacy of vaccines given to the general population with different co-morbidities, exposures and transmission levels has not been fully elucidated. Studies by Thompson et al., however, demonstrate that the authorized mRNA COVID-19 vaccines (Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273) demonstrate efficacy in "real world situations" with full 2 dose administration resulting in 90% immunization against SARS-CoV-2 infection [68] confirming mRNA vaccine Phase III trials. The CDC recommends a full 2-dose immunization with mRNA vaccine against COVID-19. The duration of immunity must also be determined with follow up studies conducted months or years after vaccination. Additionally, studies reporting on vaccine efficacy often exclude the addition of absolute risk reduction which introduces reporting bias and confuses the reader [69] with the FDA advising the use of absolute risks. Additionally, pregnant women are excluded from the preauthorization clinical trials where such patients are at increased risk of severe illness and possible adverse outcomes such as preterm birth [70]. Concerns have also emerged over the efficacy of SARS-CoV-2 vaccines to protect against the emerging VOC. Studies report however, that the BNT162b2 vaccine appears effective against the B.1.1.7 variant [71]. Certainly, the utilisation of mRNA-based vaccines offers great advantage in terms of time to development and will undoubtedly aid in future pandemics.

Conclusion

SARS-CoV-2 the aetiological agent of COVID-19 has inflicted significant damage to healthcare, economies, and communities since its emergence in December 2019. As the pandemic continues, the emergence of variants of concerns further amplifies the devastating impact of this virus across the globe with certain regions having greater difficulty with disease prevalence. In response to the pandemic, to curb viral transmission, reduce the incidence of disease and protect vulnerable persons, it is imperative to understand and implement effective control measures. Understanding the virulence factors promoting disease spread allows for the implementation of effective control measures including non-therapeutic actions such as social distancing, lockdowns and effective disinfection protocols while focus is on development and implementation of effective therapeutic and vaccination regimes. With the significant increase in biocidal application, care must be taken to prevent the over-use of disinfectants which may act as environmental pollutants, or which may accumulate causing untold damage to ecosystems. A holistic One Health approach must be considered to reduce disease prevalence while protecting human, animal, and environmental health. The emergence of

antibiotic resistant bacteria for example due to the overuse of antimicrobial disinfectants in clinical environments is of concern. Implementation of an effective vaccination programme globally with efficacy against emerging variants of concern is a necessity to curtail the SARS-CoV-2 pandemic.

References

1. Carmassi C, Foghi C, Dell'Oste V, et al. PTSD symptoms in healthcare workers facing the three coronavirus outbreaks: What can we expect after the COVID-19 pandemic. *Psychiatry Research*. 2020; 292.
2. Servidio C, Stellacci F. Therapeutic approaches against coronaviruses acute respiratory syndrome. *Pharmacol Res Perspect*. 2021; 9: e00691.
3. Chandua CV, Lingamanenib LP, Pachavac S, et al. The influence of dissonance induction and assessment reactivity in improving adherence to Covid-19 precautionary measures: a cluster randomized controlled trial. *International Dental Journal*. 2021.
4. Peterson E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis*. 2020; 20: e238-e244.
5. Ghaffari Darab M, Keshavarz K, Sadeghi E, et al. The economic burden of coronavirus disease 2019 (COVID-19): evidence from Iran. *BMC Health Serv Res*. 2021; 21: 132.
6. Nicola M, Alsaifi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *International Journal of Surgery*. 2020; 78: 185-193.
7. Xiling G, Yin C, Ling, W, et al. In vitro inactivation of SARS-CoV-2 by commonly used disinfection products and methods. *Sci Rep*. 2021; 11: 2418.
8. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell*. 2020; 182: 812-827.
9. Kampf G Brüggemann Y, Kaba HEJ, Steinmann J, et al. Potential sources, modes of transmission and effectiveness of prevention measures against SARS-CoV-2. *J Hosp Infect*. 2020; 106: 678-697.
10. Kistler KE, Bedford T. Evidence for adaptive evolution in the receptor-binding domain of seasonal coronaviruses OC43 and 229e. *Evolutionary Biology*. eLife. 2021; 10: e64509.
11. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. *Diabetes & metabolic syndrome*. 2020; 14: 407-412.
12. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020; 12: 1-5.
13. Huang Y, Yang C, Xu Xf, et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. *Acta Pharmacol*. 2020; 41: 1141-1149.

14. Tilocca B, Soggiu A, Sanguinetti M, et al. Immunoinformatic analysis of the SARS-CoV-2 Envelope protein as a strategy to assess cross-protection against COVID-19. *Microbes and Infection*. 2020.
15. Ganesh B, Rajakumar T, Malathi M, et al. Epidemiology and pathobiology of SARS-CoV-2 (COVID-19) in comparison with SARS, MERS: An updated overview of current knowledge and future perspectives. *Clinical epidemiology and global health*. 2021; 10: 100694.
16. Romano M, Ruggiero A, Squeglia F, et al. Structural View of SARS-CoV-2 RNA Replication Machinery: RNA Synthesis, Proofreading and Final Capping. *Cells*. 2020; 9: 1267.
17. Min Yuan-Qin, Mo Q, Wang J, et al. SARS-CoV-2 nsp1: Bioinformatics, Potential Structural and Functional Features, and Implications for Drug/Vaccine Designs. *Frontiers in Microbiology*. 2020; 11: 587317.
18. Karamitros T, Papadopoulou G, Bousali M, et al. SARS-CoV-2 exhibits intra-host genomic plasticity and low-frequency polymorphic quasispecies. *J Clin Virol*. 2020; 131: 104585.
19. Rausch JW, Capoferri AA, Katusiime MG, et al. Low genetic diversity may be an Achilles heel of SARS-CoV-2. *Proceedings of the National Academy of Sciences*. 2020; 117: 24614-24616.
20. Kemp SA, Meng B, Ferriera I, et al. Recurrent emergence and transmission of a SARS-CoV-2 spike deletion H69/V70. *BioRxiv*. 2020.
21. <https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-risk-related-to-spread-of-new-SARS-CoV-2-variants-EU-EEA-first-update.pdf>
22. Van Damme W, Dahake R, van de Pas R, et al. COVID-19: Does the infectious inoculum dose-response relationship contribute to understanding heterogeneity in disease severity and transmission dynamics? *Medical hypotheses*. 2021; 146: 110431.
23. Taefehshokr N, Taefehshokr S, Hemmat N, et al. Covid-19: Perspectives on Innate Immune Evasion. *Front Immunol*. 2020; 11: 2549.
24. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, et al. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine & growth factor reviews*. 2020; 54: 62-75.
25. Flerlage T, Boyd DF, Meliopoulos V, et al. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. *Nat Rev Microbiol*. 2021.
26. Mueller SN, Rouse BT. Immune responses to viruses. *Clinical Immunology*. 2008; 421-431.
27. Mortaz E, Tabarsi P, Varahram M, et al. The Immune Response and Immunopathology of COVID-19. *Front Immunol*. 2020; 11: 2037.
28. Sallard E, Lescure FX, Yazdanpanah Y, et al. Type 1 interferons as a potential treatment against COVID-19. *Antiviral Res*. 2020; 178: 104791.
29. Lee IT, Nakayama T, Wu CT, et al. ACE2 localizes to the respiratory cilia and is not increased by ACE inhibitors or ARBs. *Nat Commun*. 2020; 11: 5453.
30. Chen Z, Wherry, EJ T. cell responses in patients with COVID-19. *Nat Rev Immunol*. 2020; 20: 529-536.
31. Gubernatorova EO, Gorshkova EA, Polinova AI, et al. IL-6: Relevance for immunopathology of SARS-CoV-2. *Cytokine & growth factor reviews*. 2020; 53: 13-24.
32. Feng Z, Diao B, Wang R, et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects human spleens and lymph nodes. *medRxiv*. 2020.
33. Zhou R, To KKW, Wong YC, et al. Acute SARS-CoV-2 infection impairs dendritic cell and T cell responses. *Immunity*. 2020; 32: 132.
34. Al Huraimel K, Alhosani M, Kunhabdulla S, et al. SARS-CoV-2 in the environment: Modes of transmission, early detection and potential role of pollutions. *Sci Total Environ*. 2020; 744: 140946.
35. <https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html>
36. Meyerowitz EA, Richterman A, Gandhi RT, et al. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. *Annals of Internal Medicine*. 2020.
37. Tang JW, Bahnfleth WP, Bluysen WP, et al. Dismantling myths on the airborne transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *Journal of Hospital Infection*. 2021; 110: 89-96.
38. Barcelo D. Environmental and Health Perspective for COVID-19 An environmental and health perspective for COVID-19 outbreak: Meteorology and air quality influence, sewage epidemiology indicator, hospitals disinfection, drug therapies and recommendations. *Journal of Environmental Chemical Engineering*. 2020; 8: 104006.
39. Bourdrel T, Annesi-Maesano I, Alahmad B, et al. The impact of outdoor air pollution of COVID-19: a review of evidence from in vitro, animal and human studies. *European Respiratory Review*. 2021; 30: 200242.
40. Pedreira A, Taskin Y, Garcia MR. A Critical Review of Disinfection Processes to Control SARS-CoV-2 Transmission in the Food Industry. *Foods*. 2021; 10: 283.
41. Smit AJ, Fitchett JM, Engelbrecht FA, et al. Winter Is Coming: A Southern Hemisphere Perspective of the Environmental Drivers of SARS-CoV-2 and the Potential Seasonality of COVID-19. *International journal of environmental research and public health*. 2020; 17: 5634.
42. Engelbrecht FA, Scholes RJ. Test for Covid-19 seasonality and the risk of second waves. *One health*. 2021; 12: 100202.
43. Mileto D, Mancon A, Staurenghi F, et al. Inactivation of SARS-CoV-2 in the Liquid Phase: Are Aqueous Hydrogen Peroxide and Sodium Per carbonate Efficient Decontamination Agents? *ACS Chem Health Saf*. 2021.

44. Lin Q, Lim JYC, Xue K, et al. Sanitizing agents for virus inactivation and disinfection. *Views*. 2020.
45. Meyers C, Kass R, Goldenberg D, et al. Ethanol and Isopropanol Inactivation of Human Coronavirus on Hard Surfaces. *Journal of Hospital Infection*. 2020; 107: 45-49.
46. Steinhauer K, Meister TL, Todt D, et al. Virucidal efficacy of different formulations for hand and surface disinfection targeting SARS CoV-2. *Journal of Hospital Infection*. 2021; 112: 27-30.
47. Zucker I, Lester Y, Alter J, et al. Pseudoviruses for the assessment of coronavirus disinfection by ozone. *Environ Chem Lett*. 2021; 1-7.
48. Bidra AS, Pelletier JS, Westover JB, et al. Comparison of In Vitro Inactivation of SARS CoV-2 with Hydrogen Peroxide and Povidone-Iodine Oral Antiseptic Rinses. *J Prosthodont*. 2020; 29: 599-603.
49. Marquès M, Domingo JL. Contamination of inert surfaces by SARS-CoV-2: Persistence, stability and infectivity. A review. *Environmental research*. 2021; 193: 110559.
50. Golin AP, Choi D, Ghahary A. Hand Sanitizers: A Review of Ingredients, Mechanisms of Action, Modes of Delivery, and Efficacy Against Coronaviruses. *American Journal of Infection Control*. 2020; 48: 1062-1067.
51. Ogilvie BH, Solis-Leal A, Lopez JB, et al. Alcohol-free hand sanitizer and other quaternary ammonium disinfectants quickly and effectively inactivate SARS-CoV-2. *Journal of Hospital Infection*. 2021; 108: 142-145.
52. Auerswald H, Yann S, Dul S, et al. Assessment of inactivation procedures for SARS-CoV-2. *J Gen Virol*. 2021; 102.
53. Jinia AJ, Sunbul NB, Meert CA, et al. Review of Sterilization Techniques for Medical and Personal Protective Equipment Contaminated with SARSCoV-2. *IEEE Access*. 2020; 8: 1.
54. DeAngelis H, Grillet AM, Nemer MB, et al. Gamma radiation sterilization of N95 respirators leads to decreased respirator performance. *Plos One*. 2021; 16: e0248859.
55. Rowan NJ, Laffey JG. Unlocking the surge in demand for personal and protective equipment (PPE) and improvised face coverings arising from coronavirus disease (COVID-19) pandemic. Implications for efficacy, re-use and sustainable waste management. *Science of The Total Environment*. 2021; 752: 142259.
56. Rowan NJ, Laffey JG. Challenges and solutions for addressing critical shortage of supply chain for personal and protective equipment (PPE) arising from Coronavirus disease (COVID19) pandemic- Case study from the Republic of Ireland. *Sci Total Environ*. 2020; 725.
57. Gokhale Y, Mehta R, Kulkarni U, et al. Tocilizumab improves survival in severe COVID-19 pneumonia with persistent hypoxia: a retrospective cohort study with follow-up from Mumbai, India. *BMC Infect Dis*. 2021; 241.
58. Scavone C, Brusco S, Bertini M, et al. Current pharmacological treatments for COVID19: whats next? *British Journal of Pharmacology*. 2020; 177: 4813-4824.
59. Beigel JH, Tomashek KM, Dodd LE, et al. ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020; 383: 1813-1826.
60. Khalili M, Karamouzian M, Nasiri N, et al. Epidemiological characteristics of COVID-19: a systematic review and meta-analysis. *Epidemiol Infect*. 2020; 148: e130.
61. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19>
62. Taylor PC, Adams AC, Hufford MM, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol*. 2021.
63. Samaee H, Mohsenzadegan M, Ala S, et al. Tocilizumab for treatment patients with COVID-19: recommended medication for novel disease. *International Immunopharmacology*. 2020; 89: 107018.
64. <https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-dexamethasone>
65. Patel SK, Saikumar G, Rana J, et al. Dexamethasone: A boon for critically ill COVID-19 patients?. *Travel medicine and infectious disease*. 2020; 37: 101844.
66. <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19>
67. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021; 384: 1412-1423.
68. Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021; 70: 495-500.
69. Brown RB. Outcome Reporting Bias in COVID-19 mRNA Vaccine Clinical Trials. *Medicina*. 2021; 57: 199.
70. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *The New England Journal of Medicine*. 2021; 384: 2273-2282.
71. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *The Lancet*. 2021; 397: 1819-1829.