Frontiers of COVID-19

Scientific and Clinical Aspects of the Novel Coronavirus 2019

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Introduction

We are in the midst of a major global pandemic and due to the critical interests, the global scientific community has been desperately seeking out new research and accurate information regarding coronavirus disease 2019 (COVID-19), a contagious viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With the first, second, and in some areas, third waves of the coronavirus pandemic, our knowledge and understanding of this disease have gradually been evolving, which has resulted in revising and oftentimes revising most of our earlier understanding of the dynamics of this virus. Furthermore, we are just at the turning point in the realization of the types of antibodies produced in infected patients and the associated limitations and challenges, which are shaping the global efforts towards the effective development of COVID-19 vaccines. Therefore, we believe the timing is right to have a more comprehensive and highly anticipated book on the recent and ongoing acquired knowledge on COVID-19 and a possible roadmap on how to move forward.

This book aims to present recent clinical manifestations and findings regarding COVID-19 and the roadmap and the prospect of living gracefully alongside COVID-19 along with the existence of this virus in our societies. This work comprises the following four parts:

1. History, Pathogenesis, and Epidemiologic Background of Coronavirus
2. Clinical Observations
3. Interventions and Treatments
4. Current Trends and Future Directions

Part I: History, Epidemiologic Background and Pathogenesis of Coronavirus

Main Topics

The first part contains introductory chapters presenting the history, pathogenesis, and epidemiology background of COVID-19.

History of Coronaviruses

Novel Coronavirus (COVID-19) disease is a cascade of a family of contagious diseases, which was discovered in late 2019. The first class of illness was named the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which gave rise to a number of related variants, leading to an ongoing pandemic, which has infected over 450 million people worldwide and caused over 6 million fatalities as of March 2022 (https://covid19.who.int/).

Epidemiology and Demographics of COVID-19

The topic of SARS-CoV-2 genome relates to the importance of key encoded proteins essential for this virus to cause disease, and the diversity of SARS-CoV-2 variants that have so far emerged and their divergence from other coronaviruses.

Pathogenesis of COVID-19

The mechanism of pathology and the pathogenesis of COVID-19 has now been illustrated by several studies. The SARS-CoV-2 spike protein binds with high affinity to the human angiotensin-converting enzyme 2, or ACE2 receptor, but it can also interact with other receptors and enzymes. Following viral infection, a plethora of subsequent molecular and cellular alterations occur in the host that have been implicated in the progression of the signs and symptoms observed in COVID-19 patients.

Chapters Included

Chapter 1: Surfaces as a Source for SARS-CoV-2 Transmission

This chapter discusses the role of contaminated surfaces as a potential source for SARS-CoV-2 transmission.

Chapter 2: Humoral Immune Response in SARS-CoV-2 Infection and Its Therapeutic Relevance

This chapter covers topics such as production of antibodies secondary to SARS-CoV-2 infection, immunological memory to a future reinfection, and the role of antibodies in COVID-19.

Chapter 3: SARS-CoV-2 Invasion and Pathogenesis of COVID-19: A Perspective of Viral Receptors, Bradykinin and Purinergic System

This chapter covers the role of bradykinin and kallikrein-kinin system in the pathological findings associated with COVID-19, the involvement of purinergic signaling on the modulation of inflammatory process generated by SARS-CoV-2 infection, and possible pharmacological approaches.

Chapter 4: Genetics and Biological Characteristics of SARS-CoV-2

This chapter covers the SARS-CoV-2 genome and the diversity of SARS-CoV-2 variants and the divergence from other coronaviruses.

Chapter 5: COVID-19 Impact on Host at Pathophysiological and Cellular Level

This chapter summarizes COVID-19-associated comorbidities, dysregulated inflammation as a key factor to worsening the disease conditions, and the important molecular pathways associated with SARS-CoV-2-associated inflammation.

Chapter 6: Identification of the COVID-19 Droplet Deposition Path and Its Effects on the Human Respiratory Tract Before and After the Disease: A Scoping Novel Respiratory Mask Design

This chapter describes a well-verified real anatomical model simulating the passage of air in the human upper respiratory system, computed using high-quality Computer Tomography (CT) images, the Fluid-Structure Interaction (FSI) method, and the Discrete Phase Model (DPM) to assess the temporal and spatial motion of the deposition of virus-impregnated droplets in vitro in the upper respiratory system.

Chapter 7: SARS-CoV-2 Variants: Impact of Spike Mutations on Vaccine and Therapeutic Strategies

This chapter discusses the SARS-CoV-2 variants, their characteristics, and the efficacy of vaccine and therapeutic interventions against these variants. It also summarizes the acquired genetic alterations that have accumulated in these variants and their impact on protein structure and antigenicity.

Chapter 8: Global Biologic Characteristics of Variants of Concern and Variants of Interest of SARS-CoV-2

This chapter covers the identified variants of concerns (VOCs) and emerging variants of interest (VOIs), their biology, epidemiology, demographics, clinical manifestations, and clinical impact. It also highlights the importance of scale genomic surveillance to strengthen global health.

Chapter 9: Emergence of COVID-19 Variants and Its Global Impact

This chapter covers the nomenclature of the SARS CoV-2 variants, VOCs and notable variants, reasons for emergence of SARS CoV-2 variants, and the public health impact of viral variants.

Part II: Clinical Observations

Main Topics

The second part covers clinical observations, including symptoms (respiratory, and gastrointestinal) and complications (neurological and cardiovascular) as well as diagnosis of COVID-19 illness.

Respiratory Symptoms

COVID-19 is primarily a respiratory disease and is spread by small droplets from coughs and sneezes and reaches the respiratory tract. COVID-19 can affect the upper respiratory system (nose, sinuses, and throat) with flu-like symptoms and the lower respiratory system (airways and lungs) by causing cough with or without mucous or difficulty breathing. Runny nose, headache, fatigue, and sore throat are four fairly common signs in all COVID-19 patients. When infected with the Delta variant, sneezing, persistent cold, and loss of smell and taste are typical. With the Omicron variant, sneezing is common while loss of smell and taste are rare.

Cardiovascular Complications

COVID-19 can cause a high level of inflammation that can trigger a strong immune response and induce hyperinflammation and blood clots. The blood clots can lead to stroke and heart attacks even in young and healthy people without comorbidities.

Neurological Complications

Neurological symptoms appear in a significant portion of people hospitalized with COVID-19. These symptoms include loss of taste and smell, headaches, stroke, delirium, and brain inflammation. Evidence suggests that COVID-19 may harm the brain in different ways: attacks specific brain cells directly, reduces blood flow to brain tissue, or triggers production of immune molecules that can harm brain cells.

Gastrointestinal Symptoms

In COVID-19 patients, gastrointestinal symptoms have been reported with variable onset and severity. Symptoms include anorexia, abdominal pain, diarrhea, nausea, vomiting together with respiratory symptoms. Evidence also shows acute hepatocellular injury, indicated by elevated liver enzymes (i.e., alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase).

Psychological and Sociological Issues

Early on in the pandemic, COVID-19 patients reported an increase in panic attacks. Now, anxiety in patients is moving from panic to feeling anxious about the future. Increased anxiety caused by COVID-19 has been a factor in increasing eating disorder behaviors. Depression can be triggered when we have to isolate from others. The pandemic has also been reported to make obsessive-compulsive disorder (OCD) responses worse because the threat is no longer an unsubstantiated fear. As families quarantine in close quarters and spend more time together, the chances of marital and family conflicts increase.

Chapters Included

Chapter 10: Psychological Impacts of the COVID-19 Pandemic

This chapter focuses on the psychological impacts of the COVID-19 pandemic, where it begins with the acute effects of the pandemic in substantially increasing rates of psychological distress and symptoms of psychiatric disorders. At the end,

this chapter concludes with the promise of coping and psychological adaptation strategies, drawing from evidence reported during prior pandemics as well as early data reported during the ongoing pandemic.

Chapter 11: Spatial Epidemiology of COVID-19: Disease Risk, Prognosis, and Complications

This chapter covers the geographic, environmental, behavioral, genetic, and comorbidity differences that have influenced spatial dynamics of COVID-19 transmission and outcomes, regional and country-level hotspots, and factors that create COVID-19 hotspots.

Chapter 12: Eye Disorders and Neuro-ophthalmic Manifestations

This chapter lists the ocular signs and symptoms among COVID-19 patients, ocular surface clinical presentation, retinal vessel alterations and choroid involvement, ocular motor cranial nerves palsy, and other neuro-ophthalmic manifestations in patients with COVID-19.

Chapter 13: Evaluation and Management of Dysphagia During the COVID-19 Pandemic

This chapter discusses how a safe and reasonable dysphagia care pathway can be implemented in the context of the COVID-19 pandemic with an understanding of safety precautions, modifications of the investigation setup, and with the application of newer technologies.

Chapter 14: Gastrointestinal Manifestations of COVID-19 and Inflammatory Bowel Disease in the COVID-19 Era: Clinical Overview and Updated Guidelines

This chapter summarizes the gastrointestinal manifestations associated with COVID-19 including the pathophysiology and molecular pathways, impact on the severity of the disease, and the importance of feco-oral route of infection and viral shedding.

Chapter 15: Post COVID-19 Conditions: The New Challenge to Mankind

Post COVID-19 conditions have and will continue to have a major impact on the healthcare system in the upcoming years. This chapter covers cardiovascular complications and pulmonary embolism post-COVID and results of the first national survey in Bulgaria.

Chapter 16: Association of Alpha 1 Antitrypsin Deficiency with COVID-19 Mortality Rate

This chapter summarizes what is known about Alpha 1 antitrypsin (A1AT) (encoded by SERPINA1 gene), an inhibitor of transmembrane protease serine 2 (TMPRSS2), the major host protease that enables entry of the SARS-CoV-2 into host cells by spike (S) protein priming. It outlines the role of A1AT in the prevention of the pathogenesis of COVID-19 and associated complications and its significant potential not only in predicting the susceptibility and prognosis but also in the anti-COVID therapeutic repertoire.

Chapter 17: Social Cognition Approaches to Understanding and Changing COVID-19 Preventive Behaviors

This chapter provides an overview of the social cognition literature and interventions targeting key psychological constructs as means to adopt and maintain COVID-19 preventive behaviors. It also offers sample materials used in behavior change interventions based on social cognition theory, which could be applied across a broad range of COVID-19 preventive behaviors.

Chapter 18: Neurological Complications of COVID-19

This chapter covers neurological manifestations and neurological complications of COVID-19 (Neuro-Covid) in order to increase awareness about current and potential emerging complications and to facilitate their early recognition and effective management.

Chapter 19: The Impact of Covid-19 on Surgical Disease

This chapter summarizes wide ranging implications of COVID-19 for the practice of surgery including COVID-19-induced hypercoagulability that can affect surgical procedures, impact on trauma/acute care surgery and elective surgery, and perioperative effects of COVID-19.

Part III: Interventions and Treatments

Main Topics

The third part covers interventions and treatments of COVID-19, including oxygen and convalescent plasma therapies, antiviral agents, immune-modulating drugs, treatment of complications, vaccine and psychological interventions.

Diagnosis of SARS-CoV-2 Infection

Diagnostic tests for SARS-CoV-2 use nucleic acid, antibody (serology), and protein-based detections. Nucleic Acid Amplification Tests (NAATs, such as Reverse Transcription—Polymerase Chain Reaction) and antigen tests are used as diagnostic tests to detect current infection with SARS-CoV-2. Antigen tests generally have similar specificity, but are less sensitive than most NAATs. Correct interpretation of results from antigen tests and confirmatory NAATs, when indicated, is crucial. Antibody tests are used to detect previous infection with SARS-CoV-2 and can aid in the diagnosis of multisystem inflammatory syndrome (MIS) in children (MIS-C) and adults (MIS-A).

Current Treatments

Several drugs have been approved to treat the different stages of COVID-19, and the living WHO guideline [1] is continuously updated and practice recommendations are offered by the BMJ (https://www.bmj.com/content/370/bmj.m3379).

Chapters Included

Chapter 20: Pre-hospital Management of COVID-19: Looking for a Future Perspective

This chapter analyzes the most relevant findings confirmed by metanalyses or by randomized clinical trials (RCT), and hypothesizes their reproducibility in a pre-hospital setting. It outlines strategic pre-hospital guidelines for managing COVID-19 patients, including screening procedures and prognostic assessment, multidimensional investigations focused on both negative and positive predictors, treatment criteria, and protocols for adequate ventilation maintenance.

Chapter 21: Biotechnological Strategies in the Intervention and Treatment of COVID-19

This chapter covers the repurposed known drugs against COVID-19, the first COVID-19 vaccines, natural products, bioactive substances, and vitamins that may have the potential to treat or improve the disease progression in COVID-19 patients.

Chapter 22: Vitamin D: A Potential Prophylactic and Therapeutic Agent Against COVID-19

A common factor for progressive disease is a low-grade inflammation as seen in those with metabolic syndrome, diabetes, and cardiovascular diseases, to which micronutrient deficiencies such as vitamin D may contribute. This chapter examines the evidence supporting vitamin D's role in prophylaxis and therapeutic administration against SARS-CoV-2 infection and COVID-19.

Part IV: Current Trends and Future Directions

Main Topics

Ongoing Clinical Trials for Treatment and Vaccination

"Finding more effective and accessible therapeutics for COVID-19 patients remains a critical need, and WHO is proud to lead this global effort," said Dr. Tedros Adhanom Ghebreyesus, WHO Director-General. The WHO developed the COVID-19 Solidarity Therapeutics Trial (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments) to test potential therapies for COVID-19 with the aim of recruiting thousands of patients globally, with standardized data capture, a bigger sample size, and faster and more efficient sharing of study results.

Future Directions for COVID-19 Management in Clinical Practice and Research

Several groups around the world are conducting research to know more about the post-acute and long-term phases of COVID-19 and to differentiate the direct consequences of SARS-CoV-2 infection from hospitalization and the procedures and treatments required for care of people with severe disease of any etiology.

Post-COVID-19 or Long COVID

The World Health Organization (WHO) has developed a clinical case definition of post-COVID-19 or Long COVID [2]. It is also known as post-COVID-19 syndrome, post-acute sequelae of COVID-19 (PASC), or chronic COVID syndrome (CCS). According to the authors, post-COVID-19 "occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained

by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning." Research on post-COVID conditions is ongoing and likely to change rapidly with ongoing research.

Chapters Included

Chapter 23: Rational Repurposing of Drugs, Clinical Trial Candidates, and Natural Products for SARS-Cov-2 Therapy

This chapter covers the rationale for, and examples of, successful drug repurposing for COVID-19, SARS-CoV-2 molecular targets suitable for repurposing, computational methods for virtual screening, virtual screening results, and implications and promising leads.

Chapter 24: In Silico Drug Repositioning for COVID-19: Progress and Challenges

This chapter discusses various computational drug repositioning strategies, the challenges to the correct interpretation of existing preclinical and clinical evidence, as well as the generation of new evidence related to drug repurposing.

Chapter 25: Computationally Repurposed Natural Products Targeting SARS-CoV-2

This chapter summarizes the virtually screened natural products, such as alkaloids, sterols, peptides, polyphenols, and terpenoids, which showed antagonistic potential to host cell recognition, viral attachment and fusion through binding with various receptor-binding regions of SARS-CoV-2 spike protein for ACE2, GRP78, and NRP-1 as well as host cell transmembrane TMPRSS2.

Chapter 26: Different Platforms, Immune Response Modulators, and Challenges in SARS-CoV-2 Vaccination

This chapter summarizes how the pandemic influenced vaccine development, the implications of the route of immunization and adjuvant's choice for vaccines, and some recommendations to consider for future pandemics.

Chapter 27: SARS-CoV-2 Vaccine Against Virus: Mission (Im)possible

This chapter outlines the mutations in the viral spike protein and other parts of the virus, the implications for COVID vaccines, and gives suggestions on what the global community can do beyond vaccination, hygiene, and physical distancing.

Chapter 28: COVID-19 Vaccines Authorized by Stringent Regulatory Authorities and Vaccine

This chapter discusses the different technologies used in vaccine development and the COVID-19 vaccines developed for each modality, the different vaccines that have been approved by any national regulatory authority and the publicly available data for these vaccines, and the knowledge gaps that need to be filled to understand the important questions like durability of protection, the need for a booster, and long-term safety and efficacy against emerging SARS-CoV-2 variants.

Chapter 29: The Global Evolution of a Pandemic on Clinical Practice

This chapter summarizes the impact of the pandemic on clinical practice including regional variations in rural and urban populations, implications of backlog on hospital system recovery during the pandemic, the impact on providers and patients across many outpatient settings, employee screening protocols, use of personal protective equipment, bed allocation challenges, and reliance upon communication and social media for clinical updates.

Chapter 30: Anticipated Long-Term Neurobehavioral Outcomes Following COVID-19

This chapter addresses the less familiar encephalopathic, dementia, and behavioral syndromes that will likely be observed as more research is conducted on COVID-19 and provides guidance for clinicians who will undoubtably encounter increased volumes of patients with residual post-COVID-19 neurobehavioral changes.

Chapter 31: The Road Ahead

This chapter covers the path out of the current pandemic and the road to future directions regarding the next possible phases of COVID-19 and the long-term clinical effects of it for years to come.

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Contents

Part I
History, Epidemiologic Background and Pathogenesis of Coronavirus

Chapter 1
Surfaces as a Source for SARS-CoV-2 Transmission

Günter Kampf

Introduction

The role of contaminated surfaces as potential source for SARS-CoV-2 transmission has not been clear at the beginning of the pandemic. In the meantime, however, a lot of research has been performed, resulting in a better understanding of the relevance of surfaces contaminated with SARS-CoV-2.

Persistence of Infectious SARS-CoV-2 on Surfaces

The persistence of infectious SARS-CoV-2 on inanimate surfaces under laboratory conditions has been described for various materials. In Table 1.1, data are summarized that were obtained at room temperature. On stainless steel, SARS-CoV-2 was mostly below the detection limit after up to 7 days. Similar results were described for plastic, glass, bank notes, paper, Tyvek, nitrile, rubber, polypropylene, metal, and a disposable gown. Persistence was shorter on copper (1 h to >2 days), vinyl (12–24 h), silver (>2 days), and laminate (8 h). In the dark, the virus could not be detected anymore after 4 weeks on different materials.

A higher temperature such as 30 °C or 40 °C and a higher relative air humidity results in a shorter persistence whereas a lower temperature such as 4 °C results in a longer persistence on surfaces [5, 11, 13, 15, 16] although no major differences in persistence were described at 4 °C, 20 °C, and 30 °C in one study [14]. Higher

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Table 1.1 Persistence of infectious SARS-CoV-2 on different surfaces at room temperature

Material	SARS-CoV-2 strain	Initial viral load	Below detection limit after	References
Stainless steel	Strain USA-WA1/2020	10^{4} [a]	12 h	[1]
	Strain nCoV-WA1-2020	10^{3}–10^{4} [b]	2 days	[2]
	Strains hCoV-19/Germany/ BY-Bochum-1/2020 (B.1.1.70), VOC B.1.1.7 RKI-0026_B.1.1.7 and VOC B.1351 RKI-0029_B.1.351	10^{6} [b]	>2 days	[3]
	SARS-CoV-2 patient strain	10^{4}–10^{5} [b]	3 days	[4]
	Strain USA-WA1/2020	10^{4} [c]	4 days	[5]
	Variant England 02/2020 HCM/V/052, isolate/England/MIG457/2020 (lineage B.1.1.7), isolate/England/ H204661641/2020 (lineage B.1.351)	10^{4}–10^{5} [a]	7 days	[6]
	Isolate England 02/2020 (EPI_ISL_407073)	10^{5} [a]	7 days	[7]
	Strains hCoV-19/Germany/ BY-Bochum-1/2020 (B.1.1.70) and RKI-0026_B.1.1.7	10^{6} [b]	7 days	[8]
	Strain BetaCoV/Beijing/AMMS01/2020	10^{5}–10^{6} [b]	>7 days	[9]
	Strain CoV-19/Canada/ON-VIDO-01/2020	10^{6} [a]	>14 days	[10]
	Strain Australia/SA01/2020	10^{6} [b]	28 days [d]	[11]
Plastic	Strain nCoV-WA1-2020	10^{3}–10^{4} [b]	4 days	[2]
	SARS-CoV-2 patient strain	10^{4}–10^{5} [b]	5 days	[4]
	Isolate SARS-CoV-2/Finland/1/2020	10^{4}–10^{5} [a]	6 days	[12]
	Strain BetaCoV/Beijing/AMMS01/2020	10^{5}–10^{6} [b]	>7 days	[9]
	Strain CoV-19/Canada/ON-VIDO-01/2020	10^{6} [a]	>21 days	[10]
Glass	Strain USA-WA1/2020	10^{4} [c]	4 days	[5]
	SARS-CoV-2 patient strain	10^{4}–10^{5} [b]	5 days	[4]
	Strain HKU-001a	10^{4}–10^{5} [c]	5 days	[13]
	Strain BetaCoV/Beijing/AMMS01/2020	10^{5}–10^{6} [b]	>7 days	[9]
	Strain Australia/SA01/2020	10^{6} [b]	>28 days[d]	[11]
Bank note/ paper	Strains hCoV-19/Germany/ BY-Bochum-1/2020 (B.1.1.70) and RKI-0026_B.1.1.7	10^{6} [b]	3 days	[8]
	Isolate England 02/2020 (EPI_ISL_407073)	10^{5} [a]	5 days	[7]
	Strain BetaCoV/Beijing/AMMS01/2020	10^{5}–10^{6} [b]	5 days	[9]
	Strain Australia/SA01/2020	10^{6} [b]	28 days [d]	[11]
Tyvek	Strain USA-WA1/2020	10^{4} [c]	4 days	[5]
	Isolate England 02/2020 (EPI_ISL_407073)	10^{5} [a]	7 days	[7]
	Strain CoV-19/Canada/ON-VIDO-01/2020	10^{6} [a]	>14 days	[10]

Table 1.1 (continued)

Material	SARS-CoV-2 strain	Initial viral load	Below detection limit after	References
Copper	Strains hCoV-19/Germany/ BY-Bochum-1/2020 (B.1.1.70) and RKI-0026_B.1.1.7	10^{6} [b]	1 h	[8]
	Strain USA-WA1/2020	10^{4} [a]	4 h	[1]
	Strain nCoV-WA1-2020	10^{3}–10^{4} [b]	1 day	[2]
	Strains hCoV-19/Germany/ BY-Bochum-1/2020 (B.1.1.70), VOC B.1.1.7 RKI-0026_B.1.1.7 and VOC B.1351 RKI-0029_B.1.351	10^{6} [b]	>2 days	[3]
Nitrile glove	Strain USA-WA1/2020	10^{4} [c]	5 days	[5]
	Strain CoV-19/Canada/ON-VIDO-01/2020	10^{6} [a]	>7 days	[10]
Vinyl	Strain USA-WA1/2020	10^{4} [a]	12–24 h	[1]
	Strain Australia/SA01/2020	10^{6} [b]	>28 days [d]	[11]
Silver	Strains hCoV-19/Germany/ BY-Bochum-1/2020 (B.1.1.70), VOC B.1.1.7 RKI-0026_B.1.1.7 and VOC B.1351 RKI-0029_B.1.351	10^{6} [b]	>2 days	[3]
Laminate	Strain USA-WA1/2020	10^{4} [a]	8 h	[1]
Ceramics	Strain BetaCoV/Beijing/AMMS01/2020	10^{5}–10^{6} [b]	7 days	[9]
Wood	Strain BetaCoV/Beijing/AMMS01/2020	10^{5}–10^{6} [b]	>7 days	[9]
Rubber	Strain USA-WA1/2020	10^{4} [c]	4 days	[5]
Polypropylene	Strain USA-WA1/2020	10^{4} [c]	4 days	[5]
Metal	Strain SARS-CoV-2/ München-1.1/2020/929	10^{5} [b]	6 days	[14]
Disposable gown	Isolate England 02/2020 (EPI_ISL_407073)	10^{5} [a]	7 days	[7]

[a]PFU per coupon
[b]$TCID_{50}$ per mL
[c]$TCID_{50}$
[d]In darkness

temperatures have been described to lead to dramatic disruption of viral structural stability, especially when the heat is applied in the dry state [17]. It has been suggested that SARS-CoV-2 may be inactivated by dryness on water absorbent porous materials but sheltered by long-persisting microdroplets of water on waterproof surfaces [18].

The relevance of the rather long persistence on surfaces remains controversial. Viruses from respiratory secretions are embedded in mucus and saliva which probably contain specific antibodies against the virus, high numbers of leukocytes, and intrinsic antiviral activity because of its polyanionic charge which binds to viruses, as well as bacteria and fungi which may influence the environment around the virus

[19]. The applicability of the laboratory findings to real life is in addition doubtful for another reason. In the *in vitro* studies, a high load of infectious virus was typically applied to a small surface. The inoculum is therefore probably a lot higher than those in droplets in real-life situations. As a result, the amount of virus actually deposited on surfaces could be several orders of magnitude smaller [20].

Nevertheless, the findings obtained under laboratory conditions raised the concern that viral shedders in the public may contaminate frequent touch surfaces finally resulting in viral transmission via uncontrolled hand–face contacts. As a result, many public surfaces were subjected to disinfection, for example, in shops, museums, restaurants, public transportation, or sports facilities.

Detection of Viral RNA on Surfaces

SARS-CoV-2 RNA has been described to be quite stable on surfaces with an average of one $\log_{10}$ reduction in genome copy recovery over 21 days [7]. Laboratory data with SARS-CoV-2 show that C_t (cycle threshold) values of 29.3 (steel surface) or 29.5 (plastic surface) correlate with detection of culturable virus, whereas C_t values of 32.5 (steel surface) or 32.7 (plastic surface) correlate with the detection of nonculturable virus [21].

Surrounding of Confirmed COVID-19 Patients in Health-Care Settings

The presence of SARS-CoV-2 RNA was determined in samples obtained from surfaces in the surrounding of confirmed COVID-19 patients in health-care facilities where it is common practice to clean and disinfect surfaces in the immediate surrounding of patients regularly. That is why the surface treatment prior to sampling may well have influenced the SARS-CoV-2 RNA detection rates. In 32 of the studies, no specific information was available when the last cleaning or disinfection was done prior to sampling [21–51]. In eight studies sampling was done before the next scheduled surface cleaning or disinfection [30, 36, 52–57], and in two studies it was performed prior to cleaning with 1000 ppm sodium hypochlorite [58, 59]. In other studies surface sampling was performed at least 4 h after the last cleaning procedure [60, 61], within 4–7 h after the first daily cleaning [62], 7 h after cleaning and disinfection [63], at least 8 h after any cleaning procedure [64], before and after decontamination [65, 66], or after terminal disinfection [67].

Detection rates were mostly less than 30% (Fig. 1.1). The vast majority of C_t-values was at least 30, suggesting a low viral load and the absence of infectious SARS-CoV-2 [22, 23, 27, 30, 33–36, 38–40, 44, 46, 48, 52–54, 57, 63–66, 68].

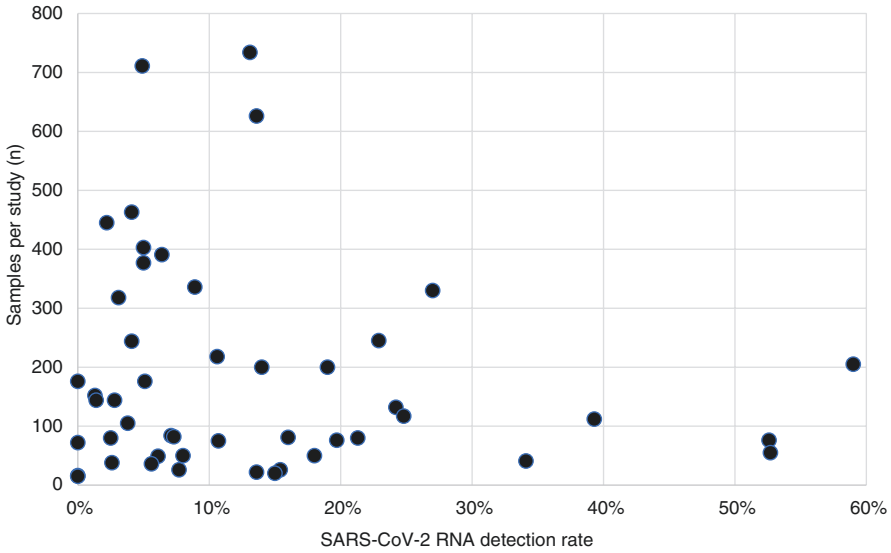

Fig. 1.1 SARS-CoV-2 RNA detection rates on surfaces in the surrounding of confirmed COVID-19 patients in health care; [21–23, 25, 27, 29–49, 51–69]

Surrounding of COVID-19 Patients in Non-Health-Care Settings

The settings were on a cruise ship during a COVID-19 outbreak [70], in rooms of COVID-19 patients [71], in COVID-19 quarantine hotels [72, 73], in domestic quarantine of COVID-19 cases [74–76], in a clinical microbiology laboratory testing for SARS-CoV-2 [77], in a nursing home during a COVID-19 outbreak [54], in a long-term care facility with 30 asymptomatic COVID-19 cases [54] and on a ferryboat during an ongoing COVID-19 outbreak investigation [54].

Samples were taken in some studies before any cleaning or disinfection procedure was carried out [54, 70, 72, 75]. In one study, however, 50% of the 428 samples were taken before the cleaning and disinfection, the other half was taken after the disinfection procedure [71]. No specific information regarding any prior treatment of surfaces was found in the remaining studies [73, 74, 76, 77].

The detection rate of SARS-CoV-2 RNA on surfaces was mostly between 0 and 20% of all samples (Fig. 1.2) with corresponding C_t values mostly >30 suggesting a low viral load and the absence of infectious SARS-CoV-2 [54, 70, 72–74, 76, 77].

Public Surfaces

Samples were collected from surfaces in various public settings such as public squares, universities, schools, parks, markets, shopping malls, stores, bank notes, water fountains and nozzles, often from high touch surfaces. The epidemiological

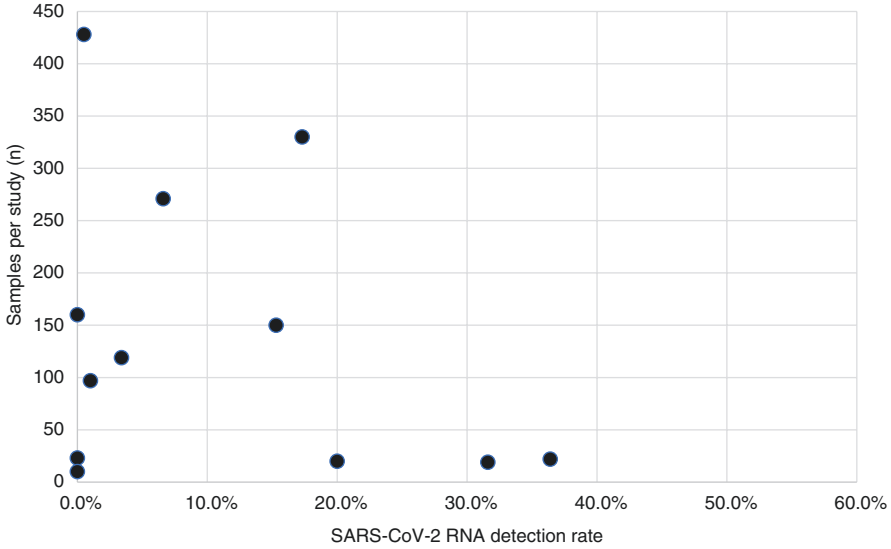

Fig. 1.2 SARS-CoV-2 RNA detection rates on surfaces in the surrounding of confirmed COVID-19 patients in non-health-care settings [54, 70–77]

situation during the study period was not described in all studies. In Brazil, the study took place in one of the regions with the highest number of notified COVID-19 cases [22]. In the USA, sampling was carried out during a regional COVID-19 outbreak [78]. In Iran, sampling was done during the early stage of a local outbreak [79]. In Italy, surfaces were samples 2–3 months after the national epidemic peak [41] or in supermarkets during a COVID-19 lockdown [80]. In China, a store was chosen for sampling after it was found to be linked to the majority of new cases in the city of Tianjin [81].

The RNA detection rates were low with 0–22.1% (Fig. 1.3), the corresponding C_t values were mostly >30, suggesting a low viral load and the absence of infectious SARS-CoV-2 [22, 78, 80, 81].

Detection of Infectious SARS-CoV-2 on Surfaces

In some of the studies the investigators tried to detect infectious SARS-CoV-2 by cell culture. In 9 of the 11 studies infectious SARS-CoV-2 could not be detected by cell culture in any sample on surfaces. Only two studies provided evidence that infectious SARS-CoV-2 can be found in the immediate surrounding of COVID-19 patients with 0.7% and 10.5% of the samples being positive (Table 1.2). A major limitation of the results of one study, however, is that seven of eight positive samples were obtained in the surrounding of only one patient with persistent cough and

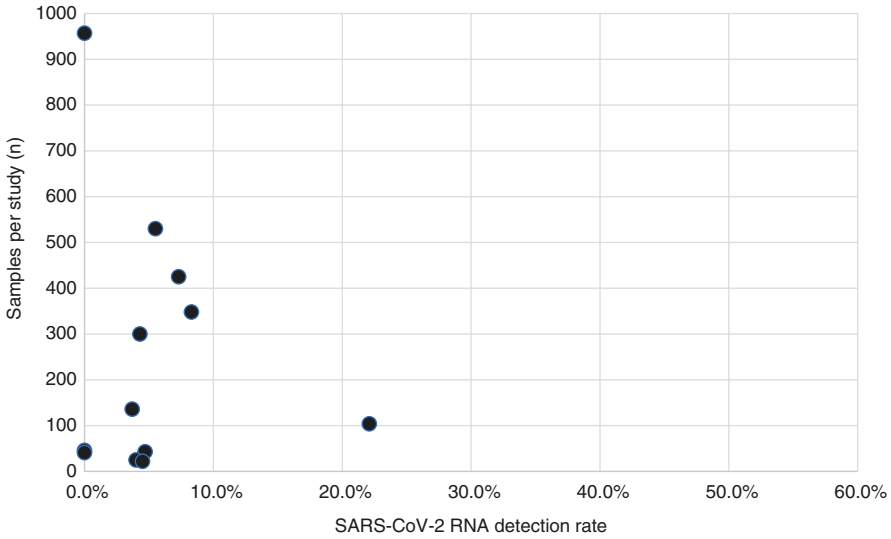

Fig. 1.3 SARS-CoV-2 RNA detection rates on public surfaces [22, 28, 31, 41, 53, 78–86]

Table 1.2 Detection rates of infectious SARS-CoV-2 and viral RNA on surfaces in health-care and other settings

Setting (country)	Types of sampled surfaces (*n*)	Proportion of viral RNA detection (%)	Proportion of infectious SARS-CoV-2 detection (%)	References
Diamond princess cruise ship during COVID-19 outbreak (Japan)	Surfaces in cabins of confirmed cases (330)	17.3	0	[70]
	Surfaces of noncase cabins (160)	0	0	
	Surfaces in shared areas (97)	1.0	0	
COVID-19 cases in isolation at home (Germany)	Surfaces in 21 households (119)	3.4	0	[74]
Treatment rooms for COVID-19 patients (England)	High contact surfaces in patient rooms (336)	8.9	0	[38]
Teaching hospital with COVID-19 patients (UK)	Various surfaces in different parts of the hospital (218)	10.6	0	[21]
Households of COVID-19-cases (USA)	Various surfaces (150)	15.3	0.7[a]	[76]

(continued)

Table 1.2 (continued)

Setting (country)	Types of sampled surfaces (*n*)	Proportion of viral RNA detection (%)	Proportion of infectious SARS-CoV-2 detection (%)	References
Severe COVID-19-cases in isolation rooms (Republic of Korea)	Surrounding of three patients (76)	19.7	10.5[b]	[68]
COVID-19 ICU (Singapore)	Various surfaces in common areas and staff pantry (75)	10.7	0	[39]
COVID-19 isolation unit (Israel)	Various surfaces (55)	52.7	0	[23]
COVID-19 isolation ward (China)	Various surfaces (50)	8.0	0	[46]
COVID-19 isolation ward (Iran)	Various surfaces (50)	18.0	0	[27]
COVID-19 cases in hospitals (Italy)	Various surfaces (26)	7.7	0	[60]

[a]Detected on nightstand of index case (corresponding C_t-value: 26.4

[b]7 of 8 positive samples obtained in the surrounding of one patient with persistent cough and frequent sputum spitting during sampling

frequent sputum spitting during sampling. It seems therefore likely that swab contamination mostly occurred by cough droplets and sputum.

Similar results were found with other respiratory tract viruses. In hospitals, SARS-CoV-1 RNA could be detected in 5.6% of 85 samples and 27.7% of 94 samples, but cell cultures for infectious SARS-CoV-1 remained all negative [87, 88]. The RNA of H1N1 influenza-A-virus could be found on surfaces of 17.8% from 90 households with confirmed infections in children, but all cell cultures were negative [89]. MERS-CoV RNA was found on surfaces of an isolation ward in 20.3% of the samples, infectious MERS-CoV was isolated in 4.1% of all samples [90]. That is why surfaces were not considered to be a relevant source of SARS-CoV-2 transmission.

The relative decline of viral infectivity on surfaces has been described to be similar with higher and lower initial viral loads. Expected levels of SARS-CoV-2 viable environmental surface contamination would therefore lead to undetectable levels within 2 days [7].

Probability of Surfaces to Be the Source for SARS-CoV-2 Transmission

A transmission from surfaces may occur via transiently contaminated hands, for example, after contact to a surface contaminated with infectious virus and followed by a hand–nose or hand–mouth contact. Several studies have analyzed the

likelihood of fomite transmission for respiratory viruses. One study highlighted the importance of aerosols for rhinovirus transmission, in contrast to a neglectable role for surfaces. In this study, two groups of men played poker, one group was sick with the common cold, the other group was healthy. The healthy group was exposed to infectious virus aerosols simply by being in the same room with the sick group. But they were restrained so that participants could not touch their faces. Cards and chips used in the poker game were transferred to a group of healthy men to play with, and they were instructed to touch their faces frequently. Interestingly, the aerosol-exposed group got sick, while the surfaces-exposed group did not [91]. In another study it was found that only a small fraction of infectious virus is usually found on hands after contact with artificially contaminated surfaces such as 0.1–16% after drying of a high initial viral load of SARS-CoV-2 [8], 1.5% with parainfluenza virus and 0.7% with rhinovirus [92]. In addition, only a small fraction of the viral load can be transferred from contaminated hands to an inanimate surface (0% with human coronaviruses, 0% with parainfluenza virus and 0.9% with rhinovirus) unless the coronavirus is presented in organic load such as feces resulting in 0–16.7% virus transfer [92, 93]. The risk of disease transmission by a hand contact with a contaminated surface followed by a single hand–nose contact is very low and has been described for rhinovirus (0.0486%) and for influenza virus (0.0000000256%) [94]. For SARS-CoV-2 it would need at least 1000 infectious viruses dropped on the mucosa [95] which is very unlikely considering the expectable loss during transfer. House flies have been described to harbor infectious SARS-CoV-2 under laboratory conditions for up to 24 h [96]. Infectious SARS-CoV-2, however, could not be detected on the surrounding surfaces after 4 and 24 h, only SARS-CoV-2 RNA. It is therefore very unlikely that house flies contribute to viral transmission via transiently contaminated surfaces. Seasonality of respiratory tract virus transmission should be considered when interpreting these results. Some factors including humidity can directly influence aerosol stability. Under tropic conditions (warm and humid climates) aerosols or droplets evaporate less water, therefore readily settle on surfaces, which could favor fomite transmission as hypothesized for influenza viruses [97].

Overall, the probability of surfaces to be the source of SARS-CoV-2 transmission is low, especially for public surfaces (Fig. 1.4).

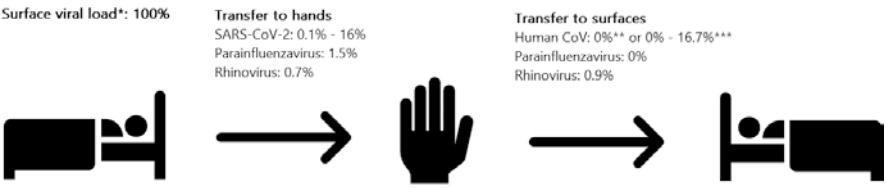

Fig. 1.4 Transfer probability of infectious respiratory tract viruses including SARS-CoV-2 from surfaces via direct contact (only data available for inanimate surfaces as target for transfer from hands) [8, 92, 93]; *assumed baseline viral load; **no organic load; ***in the presence of organic load (faeces)