SARS-CoV-2 and COVID-19: An Evolving Review of Diagnostics and Therapeutics

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Abstract

Since late 2019, Coronavirus disease 2019 (COVID-19) has spread around the world, resulting in the declaration of a pandemic by the World Health Organization (WHO). This infectious disease is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Research on the virus SARS-CoV-2 and the disease it causes is emerging rapidly through global scientific efforts. The development of diagnostics, treatments, and vaccines will be critical to mitigating the impact of the virus. Here we present a collaborative effort to organize and consolidate the rapidly emerging scientific literature related to SARS-CoV-2. We present information about the virus in the context of what is known about related viruses and synthesize studies emerging about the diagnosis and treatment of COVID-19 alongside literature about related illnesses. A broad scientific effort to understand this pandemic and related viruses and diseases will be foundational to efforts to predict possible interventions. This text is an evolving and collaborative document that seeks to incorporate the ever-expanding body of information related to SARS-CoV-2 and COVID-19.

Where to Contribute

Introduce Yourself (GitHub Issue) https://github.com/greenelab/covid19-review/issues/17

Community Chat (Gitter Room) https://gitter.im/covid19-review/community

More Info (GitHub Readme) https://github.com/greenelab/covid19-review#sars-cov-2-and-covid-19-an-evolving-review-of-diagnostics-and-therapeutics

Introduction

General Background

On January 21, 2020, the World Health Organization (WHO) released its first report concerning what is now known as the Coronavirus disease 2019 (COVID-19) [1]. This infectious disease came to international attention on December 31, 2019 following an announcement by national officials in China about 44 cases of a respiratory infection of unknown cause. The first known cases were located in Wuhan City within the Hubei province of China, but the disease spread rapidly beyond Wuhan within China and subsequently around the world. At the time of the first situation report [1], 282 confirmed cases had been identified, primarily in China, but also 1-2 exported cases had been identified in several neighboring countries (Thailand, Japan, and the Republic of Korea). One week later, 4593 confirmed cases had been identified, spanning not only Asia, but also Australia, North America, and Europe [2]. On March 11, 2020, WHO formally classified the situation as a pandemic [3]. By WHO Situation Report 61, released on March 20, 2020, 266,073 confirmed cases had been reported worldwide, with cases on every continent except Antarctica [4]. At this time, over 11,000 deaths had been reported worldwide.

[Note: Maybe add a graph here, update as new reports come out.]

COVID-19 is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a coronavirus, a family of RNA viruses known to cause respiratory and intestinal infections in humans and other species. Infectious diseases of global concern have previously been associated with coronaviruses, including Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [5,6]; however, neither of these reached pandemic status, owing to proper containment procedures (SARS) or intrinsic limitations in virus transmission (MERS). Additionally, there are four endemic human coronaviruses that rarely progress beyond the mild symptoms associated with the common cold [6]. The precise identity of SARS-CoV-2 virus was unknown until approximately January 12, 2020, when Chinese officials released its genetic sequence to aid in worldwide efforts to diagnose the disease [1]. As researchers worldwide work to characterize SARS-CoV-2 and COVID-19, information about the transmission and life cycle of the virus as well as the diagnosis and treatment of the disease is emerging rapidly. In this review, we seek to consolidate information about the virus in the context of related viruses and to synthesize what is known about the diagnosis and treatment of COVID-19 and related diseases. This is a real-time, collaborative effort that welcomes submissions from scientists worldwide.

Coronaviruses: What are they, and what do we know about SARS-CoV-19?

Coronaviruses are RNA viruses that... [Summarize relevant mechanisms for cell entry & address evidence for/against ACE2 being important]

The origin of the SARS-CoV-19 virus is not yet fully understood. Genomic analyses and comparisons to other known coronaviruses suggest that SARS-CoV-19 is unlikely to have originated from a laboratory – either purposely engineered and released, or escaped – and instead evolved naturally in an animal host [7]. Among known coronaviruses, SARS-CoV-19 has the closest overall sequence similarity to RaTG13 (~96%) found in a *Rhinolophus affinis* bat [8], while the receptor binding domain (RBD) is highly similar to that of viruses found in pangolins [9]. This suggests that SARS-CoV-19 may have originated in viral reservoirs of similar hosts, however current evidence cannot discriminate an origin of the virus before or after zoonotic transfer to humans [7].

Mechanisms of Coronavirus-driven Disease in Humans

Coronaviruses are known to cause respiratory illnesses in humans through the following possible mechanisms...

Presentation of COVID-19

Information is rapidly becoming available about the wide range of symptoms that can be associated with COVID-19 as well as the range of symptom severity, onset from exposure, and possible risk or protective factors...

Vaccines for Viruses: Strategies for and challenges to development

What information is needed to develop a vaccine? How have vaccines for other viruses such as H1N1 been developed?

Diagnostics and Therapeutics for Viruses

Two major concerns within diagnosis include the detection of current infections in individuals with and without symptoms, and the detection of past exposure without an active infection. In the latter category, identifying whether individuals can develop or have developed sustained immunity is also a major consideration.

Within therapeutics, some possible efforts include efforts to identify strategies for the management of symptoms as well as the development of antivirals...

In this review, we seek to consolidate information about efforts to develop strategies for diagnosis and therapeutics as new information is released by the scientific community.

Pathogenesis

Mechanism of Host Infection by SARS-CoV-2

This section would also be great for the introduction of zoonotic diseases which has been shown to be the origin of SARS-CoV2.

Primary Transmission and Viral Entry

[How does SARS-CoV-2 enter human cells?] [What cells are primary infection sites for SARS-CoV-2?] [What structural aspects allow for viral entry]?

Viral Replication, Spreading and Transmission

[Basic introduction into replication cycle] [What is the basic reproductive rate] [What are the routes of transmission]

Immune Response to SARS-CoV-2

[Cellular responses to SARS-CoV-2 infection] [What is causing neutropenia and lymphopenia observed in COVID-19 patients] [Antibody production against SARS-CoV-2 by patient who recovered vs patient who did not recover] [Cytokines and other soluble factors contribution to immune response]

Systems level approaches for understanding SARS-CoV-2 pathogenesis

Systems biology provides a cross-disciplinary analytical platform integrating the different omics (genomics, transcriptomics, proteomics, metabolomics, and other omics approaches), bioinformatics, and computational strategies. These cutting-edge research approaches have enormous potential to study the complexity of biological systems and human diseases [10]. Over the last decade, systems biology approaches have been used widely to study the pathogenesis of diverse types of life-threatening acute and chronic infectious diseases [11]. Omics-based studies also provided meaningful information regarding host immune responses and surrogate protein markers in several viral, bacterial and protozoan infections [12].

The complex pathogenesis and clinical manifestations of SARS-CoV-2 infection are not understood adequately yet. A significant breakthrough in SARS-CoV-2 research was achieved through the successful full-length genome sequencing of the pathogen [8,13,14]. Multiple research groups have drafted the genome sequence of SARS-CoV-2 based on sequencing of clinical samples collected from bronchoalveolar lavage fluid (BALF) [8,13] or from BALF, throat swabs, or isolates of the virus cultured from BALF [14]. Importantly, SARS-CoV-2 has significant sequence homology with SARS-CoV (about 79%) and also to some extent with MERS-CoV (about 50%) [14]. However, a higher level of similarity (about 90%) has been observed between SARS-CoV-2 and bat-derived SARS-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21), indicating a possible origin in bats [8,14].

The genome sequence of the pathogen subsequently allowed its phylogenetic characterization and prediction of its protein expression profile, which is crucial for understanding the pathogenesis and virulence of this novel viral infection. Availability of the genome sequence of SARS-CoV-2 enhances the potential for subsequent proteome-level studies to provide further mechanistic insights into the virus' complex pathogenesis. Of note, the cryo-electron microscopy structure of the SARS-CoV-2 spike (S) glycoprotein, which plays an important role in the early steps of viral infection, was reported very recently [15]. Even though no comprehensive proteomic analysis of the pathogen or of patients suffering from its infection has yet been reported, one forthcoming study has demonstrated SARS-

CoV-2 infected host cell proteomics using human Caco–2 cells as an infection model [16]. The authors observed SARS-CoV-2 induced alterations in multiple vital physiological pathways, including translation, splicing, carbon metabolism and nucleic acid metabolism in the host cells.

There is a high level of sequence homology between SARS-CoV-2 and SARS-CoV, and sera from convalescent SARS-CoV patients can effectively cross-neutralize SARS-CoV-2-S-driven entry [17]. Consequently, earlier proteome-level studies on SARS-CoV can also provide some essential information regarding the new pathogen [18,19]. Considering the paucity of omics-level big data sets for SARS-CoV-2 up until now, existing data hubs that contain information for other coronaviruses such as UniProt, NCBI Genome Database, The Immune Epitope Database and Analysis Resource (IEDB), and The Virus Pathogen Resource (ViPR) will serve as useful resources for computational and bioinformatics research on SARS-CoV-2.

Diagnostics

Current Strategies for Diagnosing COVID-19 and Similar Viral Infections

Given the heterogeneity of symptom presentation across patients with COVID-19, the development of standardized protocols for testing samples for SARS-CoV-2 is urgent. Following the release of the genetic sequence of the virus by Chinese officials on January 12, 2020, the first tests for detecting the virus were released on XX, 2020. These tests used the following approach to identify the active virus in patient samples… However, many countries have struggled to acquire the tests required to keep pace with the epidemic. [Why is it so difficult to scale up testing? What are some of the considerations?]

Possible Alternatives to Current Practices for Identifying Active Cases

[Are there other approaches that have worked for diagnosing other viruses at a rapid pace in large numbers of people?] [What are some approaches people are currently testing for detecting live viruses, especially SARS-CoV-2?]

Detection of Past Exposure and/or Sustained Immunity

[What are approaches that allow us to detect past exposure for other viruses?] [What efforts are underway to develop similar approaches for SARS-CoV-2?] [What is sustained immunity and what are the indicators?]

Limitations to Implementation of Large-Scale Testing

[Right now, reagent supply is an issue. Are there others concerns that are likely to emerge?]

Strategies and Considerations for Determining Whom to Test

[If it’s not possible to test everyone, what strategies exist for selecting who to test?] [Are these strategies likely to change over time? Presumably there are different stages of managing spread vs mitigating severity once it’s already at high prevalence?]

Therapeutics

Given the rapid predicted spread of the disease, the development of therapeutics will be critical to mitigating its effect on health and the mortality rate. Typically, therapeutics can take a few forms. First, the treatment and reduction of symptoms can result in the reduction of the severity and risk associated with an active infection. Second, the development of antiviral drugs can drive a reduced recovery time for patients by inhibiting the development of the virus once an individual is infected. Finally, vaccines present a strategy for bolstering the immune response of the populus broadly to the virus, resulting in a lower rate of infection. All three of these strategies have been valuable elements of responses to other viruses, including coronaviruses, and are being investigated by researchers at present. Additionally, there have been suggestions within the scientific community that nutraceutical or dietary supplement interventions may prime an individual's immune system to prevent or lessen the impact of RNA virus infections [20,21]. In the following sections, we critically appraise the literature surrounding the repurposing of existing treatments and development of novel therapeutics for the prevention, mitigation, and treatment of coronavirus infections.

Treatment of Symptoms

Possible background needed: -COVID-19 is characterized by... -The most severe and concerning symptoms are typically... -The symptoms most often regarded as the proximal cause of death from COVID-19 are... -Other diseases with similar symptoms include XYZ but these diseases may be different because... -Given what we know about the mechanisms of the virus and why it produces the symptoms we see, are there drugs or categories of intervention that might be relevant?

So far, some strategies for reducing the severity of symptoms have included...

Symptom Management Approach 1

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the symptom management approach.

Small Molecule Drugs for COVID-19

Antivirals are an emerging category of drugs. Unlike antibiotics, they do not kill viruses. Rather, they inhibit the proliferation of a virus. Categories may include therapies that inhibit viral proteins, inhibit viral entry, and more Antivirals have been used to treat XYZ diseases through [what mechanisms or approaches are used?]

Add a subcategory (using ####) for each category of antiviral treatment

Viral Protein Targeting Drugs

Brief background on the therapeutic.

Nucleoside Analogues

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Protease Inhibitors

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Viral Envelope

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Host Protein Targeted Drugs

Brief background on the therapeutic.

Viral Entry Receptors

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Broad-Spectrum Pharmaceuticals

Nutraceuticals

Hydroxychloroquine

Biological Drugs for COVID-19

Antibodies

Monoclonal antibodies (mAbs) have revolutionized the way we treat human diseases. As a result, they have become one of the best-selling drugs in the pharmaceutical market in recent years [**???** 10.1186/s12929-019-0592-z]. There are currently 79 FDA approved mAbs on the market including antibodies for viral infections (e.g. Ibalizumab for HIV and Palivizumab for RSV) [22,23]. Although vaccines remain the most important way to treat viral infections, their development process is long and they fail to provide immediate prophylactic protection or treat ongoing infections [24]. For that reason, neutralizing antibodies have emerged to address these shortcomings. Virus-specific neutralizing antibodies commonly target viral surface glycoproteins or host structures, thereby inhibiting viral entry [25,26]. This section discusses current efforts in developing neutralizing antibodies against SARS-CoV-2 and how expertise gained from previous approaches for MERS-CoV and SARS-CoV may benefit antibody development.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the neutralizing antibody approach.

Vaccines

Vaccines, widely recognized as one of the most significant advances in human health during the 20th century, can be used to bolser both individual and herd immunity to a virus by promoting the development of antibodies without infection. [Are vaccines available for other coronaviruses or related viral illnesses?] [What are some of the challenges to developing a vaccine? What needs to be taken into account about how the virus works?] [Are there any challenges or opportunities unique to coronaviruses and/or SARS-CoV-2?] [What are some approaches being tested or considered?]

DNA Vaccines

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

RNA Vaccines

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

Viral Particle Vaccines

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

Oligonucleotide Therapies

Background

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the neutralizing antibody approach.

Methods

Article Selection and Evaluation

The authors solicited relevant articles to be submitted via GitHub for review. Articles were classified as *diagnostic*, *therapeutic*, or *other*. Following a framework often used for assessing medical literature, the review consisted of examining the methods used in the article, the assignment (whether the study was observational or randomized), the assessment, the results, the interpretation, and how well the study extrapolates [27].

Diagnostic Papers

Methods

Reviewers began by describing the study question(s) being investigated by the article. They then described the study population, the sample size, the prevalence of the disease in the study population, if in human subjects, the countries / regions considered, the demographics of participants, the setting, and any remaining inclusion / exclusion criteria considered. They then described the reference test or “gold standard,” if one was utilized.

Assignment

Reviewers described how the new and reference tests were assigned and any further details about the study design, for example whether the diagnostic test was biased towards sicker or healthier individuals or very clear-cut positive/negative cases.

Assessment

Reviewers described how the test was performed. For example, if provided, reviewers described the technical details of the assays used, when measurements were taken and by whom for both the standard and reference diagnostic tests. They then described how individuals were classified as positive or negative and whether there was evidence that the test results were precise or reproducible when repeated more than once. Reviewers described whether there was any missing data, whether some participants underwent only one test, or whether there were individuals with inconclusive results.

Results

Reviewers reported the estimated sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV), as well as the confidence bounds around these measures, if provided.

Interpretation

Reviewers reported how well the test ruled in or rules out disease based on the population, if there were identified side effects, and patient adherence.

Extrapolation

Reviewers described how well this test will extrapolate outside the measured population.

Therapeutic Papers

Methods

Reviewers began by describing the study question(s) being investigated by the article. They then described the study population, the sample size, the prevalence of the disease in the study population, if in human subjects, the countries / regions considered, the demographics of participants, the setting, and any remaining inclusion / exclusion criteria considered.

Assignment

Reviewers described how the treatment is assigned, whether it was an interventional or observational study, whether randomization took place, etc.

Assessment

Outcome Assessment

Reviewers described the outcome that was assessed and evaluated whether it was appropriate given the underlying study question. They described whether there was any missing data, for example whether there were individuals lost to follow up. They then describe whether there were any potential sources of bias, for example lack of blinding in a randomized controlled trial.

Statistical Methods Assessment

Reviewers describe which statistical methods were used for inference and whether the methods were appropriate for the study. They then described whether adjustments were made for possible confounders.

Results

Reviewers described the estimated association between the treatment and outcome. They described measures of confidence or statistical significance, if provided.

Interpretation

Reviewers described whether a causal claim could be made. They described whether any side effects or interactions with other drugs were identified, as well as any subgroup findings.

Extrapolation

Reviewers describe how the study may extrapolate to a different species or population.

Collaborative Writing

Crowd-sourced writing with Manubot [28].

Additional Items

Competing Interests

Author	Competing Interests	Last Reviewed
Halie M. Rando	None	2020-03-22
Casey S. Greene	None	2020-03-22
Michael P. Robson	None	2020-03-23
Simina M. Boca	None	2020-03-23
Nils Wellhausen	None	2020-03-22
Ronan Lordan	None	2020-03-25
Christian Brueffer	None	2020-03-25
Sadipan Ray	None	2020-03-25
Lucy D'Agostino McGowan	None	2020-03-26
Anthony Gitter	None	2020-03-26

Author Contributions

Author	Contributions
Halie M. Rando	Project Administration, Writing - Original Draft, Methodology
Casey S. Greene	Conceptualization, Software
Michael P. Robson	Software
Simina M. Boca	Methodology
Nils Wellhausen	Writing - Original Draft
Ronan Lordan	Writing - Original Draft
Christian Brueffer	Writing - Original Draft
Sadipan Ray	Writing - Original Draft
Lucy D'Agostino McGowan	Methodology, Writing - Original Draft
Anthony Gitter	Methodology

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DOI: 10.1038/nrmicro.2016.81 · PMID: 27344959 · PMCID: PMC7097822

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Jie Cui, Fang Li, Zheng-Li Shi
Nature Reviews Microbiology (2019-03) https://doi.org/ggh4vb
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Roujian Lu, Xiang Zhao, Juan Li, Peihua Niu, Bo Yang, Honglong Wu, Wenling Wang, Hao Song, Baoying Huang, Na Zhu, … Wenjie Tan
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