

The Need for Antivirals against Covid-19

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Abstract

Recent findings have shown that the number of small and major Corona virus mutations is steadily increasing. This has major impact on the Corona policy, because the lockdowns are done to mitigate the burden of the pandemic, but they prolong the time window for the emergence of more aggressive and infectious mutants. This defense paradox may weaken the effect of vaccinations, both for the antibody response and cellular response or may lead in a worst-case scenario to an escape from natural and vaccine-mediated immunity. Antivirals typically affect sensitive procedures and structures in viruses which cannot easily mutate, i.e., are evolutionary much more stable than the surface structures that can be targeted by natural or vaccine-mediated immunity. Big data analyses have identified a larger set of potentially effective substances, but the research on these substances needs to be definitely intensified.

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1. Analysis

In March 2021, an analysis has shown that meanwhile over 680 unique variants of the receptor binding domain (RBD) of the corona virus exist¹ which corresponds to the emergence of increasingly infectious and aggressive Covid variants, such as the widespread B.1.1.7 variant first identified in the UK, the B.1.351 variant first identified in South Africa, and the P.1 variant first identified in Brazil. The doubling time of the total number RBD variants in March 2021 is estimated with approximately 72 days based on over 600,000 genome samples².

Virus mutation rates typically depend for example on the accuracy of viral enzymes that replicate nucleic acids, as SARS-CoV-2 RNA dependent RNA polymerase (RdRp), but recently another important mutant driver was found, a set of human virus defense enzymes (APOBEC, ADAR, and ZAP enzyme families) which try to damage the viral RNA; but may sometimes inadvertently cause mutations which make the virus more effective³.

This has major implications for the Corona defense strategy: while the lockdowns are done to mitigate the burden of the pandemic, they prolong the time-window for the emergence of more aggressive and infectious mutants.

This defense paradox may weaken the effect of vaccinations, both for the antibody response and cellular response or may lead in a worst-case scenario to an escape from natural and vaccine-mediated immunity⁴. Also, the immunity given by Covid vaccines is probably limited as the natural immunity in Corona-infected patients declines in a substantial proportion of patients already after several months⁵.

¹ Duarte et al 2021, Figure 1

² Duarte et al 2021

³ Azgari et al. 2021

⁴ Hofmann, Prerna et al 2021, GlobalData Healthcare 2021

⁵ Nature 2021

An intensified and quick vaccination campaign may avoid a major immunity escape by a new virus mutation, but in the long run there is a need for new antiviral medications against Covid-19. Antivirals typically affect sensitive procedures and structures in viruses which cannot easily mutate, i.e., are evolutionary much more stable than the surface structures that can be targeted by natural or vaccine-mediated immunity.

Big data analyses from various research groups have shown dozens of already existing drugs which potentially could affect Covid-19 replication. Some are antivirals already used in other settings, others may have side effects, such as cancer medications, while others have less side effects such as neurologic medications, calcium antagonists or certain antibiotics⁶.

However, when looking on the Covid-19 global research e.g., via *Google Scholar*, which provides access to medRxiv and the Covid reporting of leading scientific journals, more needs to be done to bring these findings into treatment practice.

An easy-to-conduct strategy to overcome this problem very quickly could be:

- Doing large-scale meta-analysis of patient subgroups who got one of the drugs with antiviral potential during their Covid infection and compare them to standard treated patients to identify promising candidate substances.
- Then, standard of care patients could be compared in clinical tests against the most promising substances.

As reported earlier, there is generally a significant need for new antivirals and not only for new antibiotics, as shown e.g., for the Epstein Barr Virus EBV which causes a variety of severe conditions and lymphomas⁷. There is a very urgent need for internationally coordinated (e.g., by WHO?) and intensified antiviral research before the mutants finally break through the firewall of vaccine-mediated immunity, because then the Covid-19 pandemic would go on for a very long time, definitely too long for the economy and for the lockdown strategy.

⁶ For a quick overview refer to Bahsa 2020

⁷ Biothreats and Biodefense 2018, p.16

2. Literature

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