Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

by vaccines are fundamentally distinct from those produced by naturally acquired infection. Thus, reaching herd immunity through immunization rather than infection will not only occur more quickly and with vastly less morbidity and mortality, it will likely result in greater functional immune protection for a longer duration of time (Figure 1).

Many questions remain about how herd immunity will contribute to the ultimate control of the SARS-CoV-2 pandemic and the long-term prospects for preventing future outbreaks. However, several facts are abundantly clear. Although vaccines, when available, will require months to distribute and tremendous efforts to overcome vaccine hesitancy, they still will reach the herd immunity threshold, whatever that may be, in far less time than natural infection would permit. They may produce more robust, longer-lasting, and more protective immune responses than infection. Most importantly, decades of reliable research demonstrate that vaccines are a safe and highly effective means of preventing widespread infectious diseases and are the only morally and scientifically acceptable approach for achieving herd immunity at national or global scale. Attempting to reach herd immunity through natural infection will result in devastating losses of both life and quality of life for those infected and are completely insupportable as a public health strategy for controlling a generational pandemic.

DECLARATION OF INTEREST

The author declares no competing interests

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SARS-CoV-2 Re-infections: Lessons from Other Coronaviruses

Lia van der Hoek[1,*]

Animal and human endemic coronaviruses have been known for decades, as has their capacity to re-infect. In the COVID-19 pandemic, it is key to reveal the factors that influence reinfection susceptibility. In this commentary, I provide a view on endemic animal and human coronaviruses and the correlates of protection to reinfection.

The current rapid transmission of SARS-CoV-2 shows many signs of a so called "virgin soil" pandemic, involving a population at risk that had no previous contact with a pathogen. It is expected that patients recovered from COVID-19 will have immunity, protecting them from reinfection. This acquired immunity could, in theory, be either potent or poor. Potent immunity would indicate protection, requiring a higher dose of virus to cause an infection. Poor or no protective immunity represents a situation where waning of antibodies or

[1]Laboratory of Experimental Virology, Department of Medical Microbiology and Infection Prevention, Amsterdam UMC, University of Amsterdam, the Netherlands

*Correspondence: c.m.vanderhoek@amsterdamumc.nl

https://doi.org/10.1016/j.medj.2020.12.005

Box 1. Isolates of HCoV-229E Used in Challenge and Re-Challenge Studies

Isolate ID	Year of isolation	Lab-adaptation of the virus isolate
VR-740	1962 (prototype)	No signs of lab adaptation in 1960s[2], possibly lab-adapted since 1980s[14]
LP	1965	No signs of lab-adaptation[3,7]
PR	1975	No signs of lab-adaptation[8]
TO	1975	No signs of lab-adaptation[14]
KI	1974	No signs of lab-adaptation[14]
PA	1976	No signs of lab-adaptation, likely an HCoV-NL63 isolate[14,15]

Combinations in re-challenge studies

Challenge	Re-challenge	Time to re-challenge	Combination	Protection
LP	LP	12 months	Homologous 229E-229E[7]	No (6/9)*
TO	TO	8-12 months	Homologous 229E-229E[14]	Yes (0/6)
VR-740, LP, KI, DP, TO	LP, KI, TO, or DP	8-14 months	Heterologous 229E-229E[14]	No (5/8)
PA	KI	11-13 months	Heterologous NL63-229E[14]	No (3/4)

*The total infected/total number re-challenged volunteers is indicated in parentheses.

immune cells results in a susceptibility similar to the one of individuals that have never been exposed to the virus. In the latter situation, reinfections may occur with every subsequent wave. In such a scenario, SARS-CoV-2 would become the fifth endemic human coronavirus, next to the four seasonal coronaviruses: HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63. Recently, the first cases of SARS-CoV-2 reinfections have been documented. In this commentary, I discuss these findings in light of our knowledge of reinfections by other human and animal coronaviruses.

Experimental Infections in Volunteers

It is generally assumed that neutralizing antibodies are protective and provide a defense to re-infection when subsequent waves cause re-exposure to the virus. However, it is important to realize that we have no actual proof that SARS-CoV-2 neutralizing antibodies (IgG and/or IgA) protect us from reinfections. Resistance to infection when experimentally re-exposed may reveal whether neutralizing antibodies indeed provide protective immunity. Such knowledge could hypothetically be found through human challenge studies; e.g., recruiting previously SARS-CoV-2-infected volunteers with neutralizing antibody titers ranging from high to low and determining by experimental infection whether high titers of neutralizing antibodies are associated with protection from reinfection. These studies have obviously not been done for SARS-CoV-2 and will probably not be done in the near future, because no rescue therapy which protects from severe COVID-19 is currently at hand. However, these kinds of studies can and have been done with the relatively harmless seasonal human coronaviruses, as these viruses only cause the common cold.

Neutralizing Antibodies and Protection to Reinfection

All studies that involved challenge with seasonal coronaviruses were done on adult volunteers, meaning they are, in fact, reinfection studies. This is because people experience their first seasonal coronavirus infection in the very first years of life, with seropositivity reaching plateau by the age of 4 to 6 years.[1]

In challenge studies, volunteers receive an experimental exposure to a virus via nasal drops. During the following week(s), virus shedding, increased neutralizing titers, and symptoms are documented, all seen as signs of a productive infection. These kinds of studies have been done with HCoV-229E and HCoV-OC43 from the mid-1960s to the early 1990s to study the symptoms caused by the virus or to examine immunity and therapy options. Results demonstrated that roughly half of the volunteers could not be infected by experimental exposure. Fortunately, some studies went further and examined the determinants of the observed immunity. One of the earliest studies was done with HCoV-229E in 1967.[2] Bradburne et al. found that most individuals with high pre-exposure serum neutralization titers could not be infected by HCoV-229E (only 1 out of 4 persons could be infected by isolate VR-740, see Box 1 for details on virus isolates), whereas the majority of persons with low pre-exposure neutralizing titers did become infected (78%; 17 of 22). The same association between pre-existing neutralizing antibodies in serum and protection from infection was found by Callow.[3] In addition, Callow also looked at pre-existing virus-specific IgAs and found that secreted IgAs in nasal washings are also associated with protection to reinfection.[3] Presence of IgA on the site of entry has similarly been described for animal coronaviruses, such as porcine coronaviruses. Porcine epidemic diarrhea virus (PEDV) and transmissible gastroenteritis virus (TGEV) both cause severe gastroenteritis, whereas respiratory porcine respiratory coronavirus (PRCV) causes milder symptoms in the respiratory tract. An infection by any of these viruses results in production of neutralizing IgGs and

local secretion of IgAs at the site of replication,[4] the gut for TGEV and PEDV and the respiratory tract for PRCV. Likewise, in the case of the avian infectious bronchitis virus (IBV, a *Gammacoronavirus* endemic in all countries that raise chickens, for which the eye is a site of entry), virus recognizing-IgA in the lachrymal fluid (a secretion of the eye) associates with resistance against IBV reinfection in chicken.[5] These studies strengthen the hypothesis of a supposed benefit of IgAs in protection against reinfections; however, IgAs are probably neither the only nor the most important factor. The closely related porcine viruses PRCV and TGEV illustrate this. An infection by PRCV induces no virus-specific IgA secretion in the gut, but does provide protection against TGEV,[6] indicating that other factors such as cellular immunity and/or circulating neutralizing IgGs must provide the protection here.

Neutralizing Antibodies and Severity of Symptoms

There are two additional remarks to make about neutralizing antibodies and coronavirus diseases. It is often mentioned that people that have a reinfection, as opposed to people that have their first infection, experience milder symptoms. Although this may sound plausible, one must be aware that there are no actual data for the seasonal human coronaviruses that substantiate this. A study by Callow et al., often cited in this respect, investigated re-challenge with HCoV-229E 12 months after a first challenge with exactly the same virus[7] (Box 1). The volunteers all had an asymptomatic infection, whereas their previous infection with the same isolate, 12 months earlier, showed cold-like symptoms. It must be stressed that this cannot be translated to the current SARS-CoV-2 situation, because all volunteers were adults and this was therefore not an infection into a naive person like we are now facing with SARS-CoV-2.

A second statement, said to be substantiated by the data on seasonal coronaviruses, concerns the quality of immunity raised by either a symptomatic or an asymptomatic coronavirus infection. It has been hypothesized that fewer neutralizing antibodies are produced if a coronavirus infection occurs without symptoms. It needs mentioning, however, that this hypothesis is not strengthened by data obtained from seasonal human coronaviruses. Kraaijeveld et al. and Callow et al. showed that rising neutralization titers are not dependent on the severity of symptoms. Even asymptomatic productive infections show antibody rises in the volunteers.[7,8] Whether the antibody response raised by a symptom-free infection was of lower quality (e.g., lower titers or less secreted mucosal IgA) is an important question; however, it has not been examined for the seasonal coronaviruses.

T Cell Immunity

The role of T cells in vulnerability to reinfection is another important topic also not yet studied for the seasonal human coronaviruses. The very first data on virus-specific T cells recognizing seasonal coronaviruses are being generated only now, more or less as a by-product of looking at cellular immunity recognizing SARS-CoV-2. Whether CD4 or CD8 T cells play an important role in clearing human seasonal coronaviruses during the acute phase, or if immune memory B and T cells result in less disease upon reinfection, remains unknown. Cellular protection against reinfection has been investigated for one animal coronavirus. Seo et al. showed that transfer of CD8-enriched IBV-primed T cells to chicken that were subsequently IBV challenged the next day provided protection by reducing infections or, when infected, disease severity.[9]

Duration of Immunity to Seasonal Coronaviruses

The first human coronaviruses discovered, HCoV-229E and HCoV-OC43, were identified in the mid-1960s, and two additional seasonal coronaviruses were identified in 2004 and 2005, HCoV-NL63 and HCoV-HKU1, respectively, bringing the total to four human seasonal coronaviruses. With more than 50 years of research on seasonal coronaviruses, one would expect a wealth of knowledge on reinfections from which we can now benefit. Indeed, there are the aforementioned seasonal coronavirus challenge studies that are particularly informative, yet other early studies that looked at sero-surveillance to monitor natural reinfections are unfortunately of less use. These studies were all done prior to 2004, and because they used full virus ELISAs, which have considerable cross-reactivity for viruses within a genus, no distinction between the alphacoronaviruses (HCoV-229E and HCoV-NL63) and betacoronaviruses (HCoV-OC43 and HCoV-HKU1) can be made. Therefore, only serological surveys that use species-specific serological tests, recognizing antibodies induced by one of the four seasonal coronaviruses, are informative. We very recently performed such a study in healthy adults to determine the frequency of reinfection by the same coronavirus species and found that protection to reinfection may last for one year.[10] Another recent study, in healthy volunteers including both children and adults, had the unique opportunity to look at reinfection via PCR screening in respiratory samples obtained weekly. Galanti and Shaman found that reinfections by the same seasonal coronaviruses can occur in a time window shorter than 1 year.[11] Regrettably, genetic information on the re-infecting strains was not obtained in either of the two studies mentioned above, and it remains therefore uncertain whether the reinfections were realized by viruses belonging to different

Box 2. Seasonal Coronaviruses versus SARS-CoV-2

Characteristics shared between seasonal coronaviruses and SARS-CoV-2

- HCoV-OC43, HCoV-HKU1, and SARS-CoV-2 are in the same genus (*Betacoronavirus*)
- Primary site of infection is the upper respiratory tract for all seasonal coronaviruses and SARS-CoV-2
- Receptor ACE2 is used by HCoV-NL63 and SARS-CoV-2
- Most infections are mild and do not require hospital uptake
- One genetic type is currently circulating for SARS-CoV-2, which is also observed for HCoV-229E (at one moment in time)

Differences between seasonal coronaviruses and SARS-CoV-2

- COVID-19 can be severe whereas diseases associated with seasonal coronaviruses are rarely life-threatening
- The first wave of infections by SARS-CoV-2 were in naive persons, whereas seasonal coronaviruses enter primed adults
- SARS-CoV-2 is easy to culture with fast production of progeny virus, and many SARS-CoV-2 isolates are available for research. Seasonal coronaviruses are difficult to culture in cell lines. Only three isolates of seasonal coronaviruses are as yet available for research: the Amsterdam-1 isolate of HCoV-NL63, VR-740 of HCoV-229E, and VR-1558 of HCoV-OC43
- Thus far, SARS-CoV-2 isolates in humans belong to the same antigenic cluster. In contrast, there are two co-circulating types of HCoV-OC43, two co-circulating types of HCoV-NL63, and three co-circulating types of HCoV-HKU1, and these genetic diversities within species may represent different antigenic variants

genetic clusters of coronavirus species (see Box 2).

Duration of Immunity to Animal Coronaviruses

Human coronaviruses as well as animal coronaviruses are able to re-infect their hosts. Coronavirus infections have been studied in pigs, chickens, cows, dogs, and cats, but unfortunately animal coronavirus studies have rarely monitored natural reinfections, as most of these animals tend to live a relatively short life. Studies on porcine, bovine, and avian coronaviruses, for example, investigated susceptibility to infection after vaccinations or experimental infections, yet did not investigate challenge or reinfections after a long period (>1 year). The only studies that had >1 year follow up and looked at natural reinfections are the studies done on feline coronavirus (FECV). This virus belongs to the *Alphacoronavirus* genus, is a close relative of TGEV, and produces mild or subclinical gastrointestinal symptoms in cats, yet can evolve into a life-threatening peritonitis. Because domestic cats live relatively long lives, reinfections could be studied. In one exceptional example in which a community was followed for more than 10 years,[12] 26 cats were regularly examined for rises in FECV-antibodies. The study found frequent reinfections, even up to three times in two cats. The shortest interval between subsequent infections was 11 months.[12]

Can Seasonal Coronaviruses Be Used as Model Systems?

The burning question is whether we can translate the abovementioned 1-year protection observed for mild endemic coronavirus reinfections to the current SARS-CoV-2 infections and development of COVID-19. There are definitely commonalities from which we may anticipate that some translations can be made, yet also some important differences (see Box 2). The first and major difference is that infections by SARS-CoV-2 can be much more severe than the seasonal coronaviruses. Proper immunological memory may be dependent on sufficient antigen exposure, and a mild COVID-19, similar to the common cold caused by the seasonal coronaviruses, may perhaps result in a 1-year protection to reinfection. In that line of thinking, persons who experienced severe COVID-19 may be protected for longer than 1 year, yet patients with mild or asymptomatic COVID-19, which comprise the majority of infections, may not. The second difference is that SARS-CoV-2 infections are new in the population, whereas seasonal coronaviruses infect previously primed adults. As mentioned above, children experience the first seasonal coronavirus infections in their first years of life. This first infection is generally mild or may even occur unnoticed, and in subsequent years repeated infections occur. We may expect that immunity to seasonal coronaviruses, due to this repeated exposure, has matured by adulthood. For SARS-CoV-2, which is now introducing itself for the first time, it remains uncertain if a single encounter is sufficient to mount good immunological memory.

Increased Susceptibility to Reinfection by Genetic Variants

In theory, if new SARS-CoV-2 strains with sufficient antigenic differences evolve, immunity may only protect against a certain antigenic variant, allowing infections with other strains. Fortunately, there is minimal antigenic diversity in the SARS-CoV-2 genome sequences today. Thus far only two mutations have reached the current consensus: the D614G mutation in the Spike and the P4715L in the ORF1ab protein. These mutations do not affect immunogenicity and all isolates co-circulating at this moment may therefore be regarded as the same type. This is like the situation for HCoV-229E. This virus, unlike the other seasonal coronaviruses, shows only chronologically distinct strains but no co-circulation of genetically different types[13] (see Box 2). Considering that the HCoV-229E reinfection situation may be the situation ahead of us for SARS-CoV-2, a study by Reed, investigating HCoV-229E reinfections, becomes highly relevant. Reed found that after 8–12 months, volunteers were still immune, since there were no infections when the same isolate (see Box 1) as the one in the first challenge, was used in a

re-challenge.[14] Next to the homologous re-challenge, Reed also described a heterologous challenge/re-challenge experiment, 8–14 months apart using various combinations of isolates (Box 1). Cold symptoms and virus shedding were seen in 5 out of 8 volunteers upon heterologous re-challenge. In comparison with the homologous re-challenge, this shows that strain variation is influencing susceptibility to re-infections; yet, the exact combinations of virus isolates were unfortunately not provided in the manuscript. It remains therefore unknown how large the chronological distance was between strains as well as whether lab-adaptation may have influenced the results. One of the isolates used, VR-740, became lab-adapted in the 1980s, hardly causing disease,[14] and may therefore not have been the best candidate virus in either challenge or re-challenge experiments. The third and final re-challenge experiment done by Reed was with an isolate, at that time suspected to be a HCoV-229E strain,[14] yet in hindsight most probably HCoV-NL63.[14,15] The heterologous *Alphacoronavirus* challenge showed a productive HCoV-229E infection in 3 of the 4 individuals previously primed with HCoV-NL63[14] (see Box 1). From this it can be concluded that distinct strains of HCoV-229E, and the two distinct *Alphacoronavirus* species, may provide limited cross-immunity. Translating this knowledge to the COVID-19 situation reveals that we may expect little cross-protection by immunity raised by the seasonal coronaviruses. Furthermore, there will be an increased risk of reinfections when antigenically different SARS-CoV-2 strains emerge with time.

Conclusions

Endemic animal and human coronaviruses have a common characteristic: they re-infect their host. Although endemic coronaviruses have been known for decades, knowledge concerning the factors that influence susceptibility to reinfections and the severity of disease is still somewhat limited. This is in part due to the early discovery of HCoV-OC43 and HCoV-229E. At that time (mid-1960s) it was not known that half of the human seasonal coronaviruses were still unidentified. Sero-surveillance studies done before 2004/2005 (the dates of discovery for HCoV-NL63 and HCoV-HKU1) and some challenge studies with HCoV-229E are thus difficult to interpret, as HCoV-NL63 may unknowingly have interfered in HCoV-229E studies. Still, some animal and human challenge studies are highly informative, showing the importance of neutralizing antibodies (IgG and IgA) and $CD8^+$ T cells in protection against reinfections.

Whether the current SARS-CoV-2 reinfection case reports that have been presented, some as early as a few months after the first encounter, are the rule or the exception is unknown. Data on the seasonal human coronaviruses show a protection of 1 year post infection, perhaps longer. If this is also the case for SARS-CoV-2, then we are now facing SARS-CoV-2 reinfection exceptions. However, the 1-year-or-more protection for the endemic human and animal coronaviruses may have been shaped by repeated infections from childhood on, different from what we are currently facing with SARS-CoV-2. Thus, repeated exposure may be needed to reach immunity that lasts for more than a few months. Boosting by a vaccine may then tentatively result in such an effective immunity, hopefully as active as natural exposure. Safe and effective vaccines, ideally combined with antivirals to prevent severe disease for those not immune yet, are therefore the hope we have, releasing us from lockdowns and other physical distancing policies.

ACKNOWLEDGMENTS

Major thanks to Arthur Edridge for extensive reading and useful discussions and to Paul Britton for critical reading and valuable suggestions.

DECLARATION OF INTEREST

The author declares no competing interest.

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Pandemic Vaccines: How Are We Going to Be Better Prepared Next Time?

Florian Krammer[1,*]

In response to the SARS-CoV-2 pandemic, we are currently witnessing the fastest vaccine development in history. While these vaccines will now make a significant impact on ending the pandemic, they were needed much earlier. Here I discuss how to ensure that vaccines will become available within 3-4 months after a new outbreak.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 in Wuhan, China, and caused a global coronavirus disease 2019 (COVID-19) pandemic.[1] Since then more than one million people have died globally, millions have been infected, and in many countries we are seeing signs of societal disintegration. The global economy has taken a major hit and businesses in many areas including tourism, hospitality, and the airline industry are fighting for their survival or have already gone bankrupt. Daily life has become difficult, even for people who have not been infected or have lost loved ones. In addition, while countermeasures like social distancing, wearing face masks, and restrictions on large gatherings (especially indoors) can help to keep infections low if effectively implemented, the populations in many countries are getting tired and are often unwilling to comply to countermeasures, let alone complete lockdowns.

Vaccines against infectious diseases have been one of the greatest successes in human history, effectively reducing disease burden for many pathogens. They have even allowed us to eliminate a human virus (smallpox) and a livestock virus (Rinderpest virus) from the face of the earth. When the sequence of SARS-CoV-2 was made openly available by Chinese scientist on January 10, 2020, a race to develop a vaccine began.[2] This was not a race of vaccine candidates against each other, but a race against the virus. SARS-CoV-2 vaccine development is moving ahead at record speed. Based on important development work already done on other coronaviruses,[3] the first phase 1 trial was started on March 16, 2020,[4] the first individuals were enrolled in phase 3 trials in summer 2020, and results showing high effectiveness of two of these vaccines were recently reported. This speed of vaccine development is unprecedented, and the vaccines will likely be key in ultimately resolving this situation. They will also save millions of lives. However, vaccines were needed much earlier, as early as possible (Figure 1A). While it is unlikely that vaccines would have stopped the virus from going global, a well-prepared infrastructure capable of producing vaccines 3–4 months into the outbreak (in March or April) would have saved many lives and would likely have normalized the situation in many geographic areas by now (Figure 1B). Still, without vaccines, countries in the Northern hemisphere experience a strong increase in cases during the fall, even in countries that controlled the initial wave well. Here, I will try to provide a strategy that might allow us to be better prepared in the future from a vaccine perspective.

Overall Strategy

Many different viruses may cause a pandemic in the future, but we know which virus families have the most potential. And it is viruses that spread from human to human via the respiratory tract that we worry about the most, since this is a transmission route that is hard to stop. Viruses that use other transmission routes can be highly problematic as well but might be impacted much more by non-pharmaceutical interventions. From each of the identified virus families, which should certainly include the *Paramyxoviridae*, *Orthomyxoviridae*, and *Coronaviridae* families, a handful of

[1]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

*Correspondence: florian.krammer@mssm.edu

https://doi.org/10.1016/j.medj.2020.11.004