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Public Policy and Lessons from Immunity in a COVID World

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ABSTRACT

To counter perceived viral threats, government organizations have the task of steering public opinion towards behavior that shapes the immunity of the population. This could take the form of vaccine campaigns and/or 'non-pharmaceutical interventions'. Vaccines are accepted as the most effective means in thwarting the severity of an infection both individually and throughout a population. The success or failure of campaigns however hinges on the messaging of the objectives, public trust, and above all the science that substantiates the campaign. Some consider the recent Coronavirus Disease 2019 Pandemic as one insufficient in clear and consistent messages. At the level of communication, confusion stemmed from the complexities of 1) asymptomatic and presymptomatic transmission, 2) the merits of natural and acquired immunity, 3) The relevance of herd or community immunity, as well as 4) correct information regarding the benefits and risks of necessary vaccination. Here, we review the basis and inconsistencies in the therapeutic and infection messages relevant to immunity concepts that lent to public confusion associated with this and perhaps future pandemics.

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has certainly been a challenge globally. We have had three epidemic coronaviruses — the original SARS (caused by SARS-CoV), MERS (caused by MERS-CoV) and SARS-CoV-2 [1]. It is speculated that four endemic coronaviruses have circulated in humans for hundreds to thousands of years. As SARS-CoV-2 pandemic is transforming, this is now classified as an endemic virus [2]. Yet there is no specific definition of what endemic means from a policy perspective [3]. As with most pandemics, a great hope was put on a quick development and wide application of a vaccine. Clearly vaccines have revolutionized global health with subsequent impacts economically, on social perspectives and public policy actions [4-6]. Indeed, vaccines have played a key role in controlling the global pandemic of SARS-CoV-2. The highlights of the history of vaccination, technology associated with them, and the emergence of vaccine campaigns have been discussed by numerous authors [7-11].

Of no less importance is the politics of vaccination [12-16]. It is within this realm that festers miscommunication, disinformation and confusion contributing to vaccine hesitancy [17-21]. The politicization of science is noted to have the potential to limit the positive impacts that scientific advances can offer when people reject sound and beneficial scientific advice [19]. But scientists can also play a role in contributing to politicization [22]. From the perspective of policy makers, scientific debate and political debate can become indistinguishable. Care must be taken because such a conflation can limit the role of science in the development of creative and feasible policy options [22] .

The aim and scope of this review is to outline essential elements or lessons associated with vaccination that affect trust in public health messaging and concepts associated with immunity to the virus. Smallpox provides an informed backdrop because of the immune concepts that emerged relevant to forward thinking of viral infections, and the controversies generated sharing similarity in the underlying societal misgivings in dealing with COVID [23]. A bright spot in the smallpox epidemics of the late 19th and early 20th century paved the way for the United States (U.S.) Congress to enact what was called the Biologics Control Act, which laid the foundation for vaccine safety regulations that are still in effect today. The way the smallpox epidemic was thwarted has to some extent been mirrored in present day dealings with COVID through compulsory vaccination [24], quarantine [25] and public health surveillance [26], as well as letting the natural course of the disease play out [27].

The Beginning of Modern Day Vaccination

The emergence of the importance of immunity to Public Health is often associated with Edward Jenner [28] and the prevention of smallpox [29]. Vaccines have eradicated smallpox, slashed child mortality rates, and prevented lifelong disabilities [30]. Conceptually, it is thought Jenner hypothesized that prior infection with cowpox could lead to cross protection against smallpox. The host immune response to the virus associated with cowpox is usually sufficient to control the viral infection. However, there is no evidence for such rational thinking at the time [29]. Instead, it appears the historical evidence for the emergence of vaccination speaks to antidotal observations including empirical knowledge from deep antiquity from China and the peoples of the Ottoman Empire in more recent time (18C) [31]. The most important link between cowpox exposure and smallpox protection was the observation that only cowpox infection shortly before inoculation was needed, and only when a large group of individuals were inoculated together could the existence of several resistant individuals become apparent. It is noted that others, before Jenner, recognized this antidotal relationship [32].

Whatever the historical truth, dealing with smallpox sparked the advancements in modern immunization strategies. We now understand that the cowpox virus is genetically and antigenically related to the Variola viruses that cause smallpox [33]. Understanding those proteins that induce cross-reactive immune responses that are protective from infection provide important indications for the design of new-generation recombinant subunit vaccines against *Orthopoxviruses* in particular [34] and perhaps as a technology platform for other viruses and general immune responses. Smallpox being the first target of a vaccine approach is now considered eradicated and since 1976 smallpox vaccinations have ceased as a public health measure. There are some lessons from the smallpox virus and the ensuing vaccination approach. But the all or nothing nature of the smallpox infection and immunity facilitated the positive outcome of that campaign. In contrast, current immunology and vaccinology proved helpless, for instance, in the case of the HIV vaccine. Consequently, the successful prevention of smallpox and other diseases by vaccines is not transferable to all infections. Unfortunately, the infection with SARS-CoV-2 proved to be one of the latter.

Let's dissect what is learned from the smallpox campaign and how it maps onto the COVID-19 pandemic. The first lesson is to decide if the goal is to prevent, treat or cure a disease. How one goes about these distinct objectives is very different, yet they can be immunologically based. The second lesson stems from spotting a person with smallpox associated lesions making it easy to diagnose. What do we do when an individual has less apparent symptoms. A third lesson is the necessity for a long-term immune response on the order of years required to contribute to the concept of herd or community immunity. A fourth lesson is species virus interaction and specificity. Should we contrast immunity acquired after infection (often mislabeled as natural immunity) with immunity acquired after vaccination? Each of these aspects proved also a cause for mistrust and hesitancy. Thus, a fifth lesson is informing and listening to the public will. The public must be provided a rational, scientific account of the risks and, subsequently, have trust that the means proposed to do so constitute the right approach. Likewise, the public must be included in the dialogue reflecting horizonal communication – not just vertical communication- in risk reduction, learning and planning. In the following we address these lessons in a COVID World.

Lesson 1- What's the target objective?

The primary strategies to thwart infectious diseases include controlling the source of infection, blocking the route of transmission and protecting the susceptible [35]. Among therapeutic strategies, vaccines, are an effective means to protect the susceptible and block disease transmission [36]. From a target perspective there are several overarching considerations that focus on the immune response to a virus and the pathogenesis of the infection [37]. First, we are interested in the type of population to be immunized [38] or the percent of individuals we want to reach [39]. Second, the characteristics of the vaccine to reach that population, and third, the outcome measures or read outs to define vaccine efficacy [40]. Yet, from a vaccine perspective, the merit of a vaccine relies heavily on the evaluation of proxies of a vaccine's effect on transmission of a virus, on prevalent infection and on the viral load.

We must first distinguish vaccines in the context of therapeutic versus prophylactic vaccines. This distinction defines the population being reached. Sick or not sick. Prophylactic vaccines are administered to individuals as a precautionary measure to prevent the infection or disease while therapeutic vaccines are administered after an individual is already affected by the disease or infection. Clearly for smallpox, the goal of vaccination was to prevent infection and thereby prevent transmission, hence the vaccine was prophylactic. For COVID-19 convalescent antibodies were developed to thwart the infection process [41]. Hence, a therapeutic approach. Even though therapeutic vaccines for viral diseases may not be advantageous, some developments of therapeutic approaches have been suggested and tested for infectious diseases [42]. In either case focusing on understanding the differences in the immunizing and non-immunizing immune responses to natural infections and corresponding shifts in immune ontogeny are crucial to inform the next generation of infectious disease vaccines [43].

Second, is the duration of response. Smallpox vaccination has the potential to provide immunity for a very longtime [44]. Historically, the vaccine has been effective in preventing smallpox infection in 95% of those vaccinated. Hence, the objective of the modern-day smallpox vaccine campaign was to vaccinate a high percentage of the global population to thwart the transmission process with the intent to eradicate the disease. This was a stated message by the World Health Organization. It was demonstrated that the cell-mediated immune response following direct challenge with vaccinia mechanistically exhibited a strong virus-specific $CD4^+$ and $CD8^+$ T-cell response, which declines slowly with an average half-life of 8–15 years [44]. In contrast to the cell-mediated response, the humoral immune response was shown to remain steady for as long as 75 years and could therefore have a greater role in smallpox immunity than previously thought. For COVID-19 antibodies from vaccination (regardless of the vaccine platform) wane, on average, after 5–6 months [45,46], providing a justification for booster injections. The constantly changing circulating SARS-CoV-2 variants, due to its tendency of mutations with the ability to escape the antibody response, necessitates revaccination with a suitable vaccine [47,48].

Third what's the intended use? Within 9 months of COVID-19 reaching pandemic proportions, SARS-CoV-2–targeted mRNA vaccine technologies received emergency regulatory approvals and were distributed to many developed countries [49]. The stated primary goal of the U.S. Center for Disease Control (CDC) in 2019 for public health practice and continues today is to prevent severe illness and death (https://www.cdc.gov/mmwr/volumes/71/wr/mm7133e1.htm) . Consequently, vaccine results were presented in terms of 4 main areas: effectiveness of preventing infection, illness (death), hospitalizations and limited observations on preventing onward transmission of the virus [50-54]. This message was echoed by the Canadian CDC (https://www.quebec.ca/en/health/advice-and-prevention/vaccination/covid-19-vaccine#). Results soon put into perspective the challenges associated in defining if a COVID-19 directed vaccine works [55] and which populations should a vaccine be directed towards – elderly, those with comorbidities or everyone [54].

One can argue that antibody targeting the SPIKE protein was a means to block the interaction with the angiotensin-converting enzyme 2 (ACE2) receptor of the host to inhibit the infection process. While the SARS-CoV-2 virus requires ACE2 to infect cells, the precise relationship between individual(s) ACE2 levels, ACE2 polymorphisms, viral infectivity and severity of infection are still not well understood. Targeting this interaction falls under the premise associated with mechanisms of antiviral drugs. This includes the increase of a cell's resistance to a virus and suppression of virus adsorption on the cell or it is entering the cell [56,57]. The development of antibody cocktails used therapeutically highlight this point [58]. Therefore, targeting the ACE2 interaction was going to positively impact on illness and presumably death but not prevent virus transmission directly, but indirectly. This is especially true when considering comorbidity status and age of individuals in the early days of COVID-19 infections. But this again could be a confusing message for the public since the public generally thinks that vaccines prevent the spread of infection, with images of smallpox, polio and measles in their mind's eye (https://www.pewresearch.org/science/2023/05/16/americans-largely-positive-views-of-childhood-vaccines-hold-steady/#:~:text=Fewer%20than%20half%20(43%25),coronavirus%20vaccines%20outweigh%20the%20risks) .

Fourth, dealing with viral spread. Unfortunately, epidemic control was seriously hindered by public opposition to vaccination, or vaccine hesitancy, reflecting a lack of trust that includes low confidence in government advice, and among other issues, extensive misinformation on social media [59-62]. These topic areas soon found their way into health policy and social media discussions. Accusations of misleading the public and policymakers as to whether covid vaccines could halt the spread of the virus were rampant based upon the lack of detailed clinical studies showing virus transmission can be halted and general fear of a perceived new vaccine platform. News and social media focused on emerging mandates such as vaccine passports and their ethical and legal basis [62]. The wording of Passport messaging implied that vaccination would prevent the spread of virus [63-65], while on the other hand social media focused on a Pfizer executive accurately stating that studies of the vaccine's effect on virus transmission from person to person were not performed during the original clinical trials of the company's vaccine.

At the time both European and U.S. Food and Drug Administration (FDA) agencies emphasized that preconditional marketing did not require vaccine manufactures to show a vaccine candidate prevented onward transmission. Manufactures did not address respective vaccine impact on transmission during clinical trials is not unusual, because transmission is a complex metric to measure. It can be very difficult to evaluate a vaccines impact on transmission, typically requiring a randomized, blinded, placebo-controlled study. Often benefits not studied at time of approval become clearer after a vaccine is used. Specific studies post-approval are often necessary to show prevention of infection (asymptomatic cases), long-term protection and transmission in a community. For the lay public this could be a confusing since many have shown they understand the importance of clinical trials but not aware of the process [66].

Still perplexing are some statements made by scientists can propel media conclusions [67]. In this age where the mantra is "follow the science" one can find opening sentences in manuscripts like "Vaccination rates are still insufficient to prevent the spread of COVID-19, so immunity must be increased among the population in order to reduce the virus' spread and the associated medical and psychosocial effects" [68]. The word "spread" implies that vaccination will block transmission as indicated in CDC write ups "When an infectious agent moves to another host, we call this transmission" (https://www.cdc.gov/scienceambassador/videos/how-does-disease-spread-quick-learn-transcript.pdf) . In 2021 epidemiological data from the early studies indicated excellent efficacy and safety profile for the various COVID-19 vaccines. However, at that time there were few data from studies on the effect of decreasing the probability of infection of vaccinated subjects compared to unvaccinated subjects [69]. It was shown that the viral load in vaccinated and COVID-19-positive persons, could be the 2–4 times lower than in unvaccinated persons [70]. Based on limited studies it was anticipated that a decrease in viral load makes a person less infectious and hence thwarted virus transmission, but such a conclusion was on limited numbers of individuals and didn't anticipate the effect of variants on immune escape.

While safe and an effective way to protect oneself, it is not a given that it protects those around the vaccinated individual. Herd or community immunity is now argued will not be achieved [71]. Regardless of whether messaging emanates from public health authorities, Government officials, scientists, private sector or vaccine companies the messaging for clinical science results and expectations must be consistent and credible. Otherwise, mistrust emerges which is influenced by factors such as misinformation, complacency, convenience and confidence [72].

Lesson 2- More reasons to be vaccinated?

While for smallpox one can observe who is sick and who is not, for COVID-19, characterizing early clinical symptoms was unsuccessful. In the early days of the pandemic there were many models attempting to predict the number of potential deaths if no therapeutics were available [73]. Because of this, asymptomatic testing was initiated. Viral RNA could be detected in blood. If people became ill, they do so between 2 to 14 days post exposure. Shortly after their illness anti-viral antibodies and T cells could be detected in peripheral blood. The kinetics of this response however varies from person to person with the acquired immune response to the virus waning quickly. This relatively short-lived response contributed to the virus hanging around in the population. Again, the viral load and viral shedding especially compared to the infectious dose remained unclear for some time.

Related studies highlighted a progressive shortening of the virus incubation period, serial interval, and generation time, which can lead to epidemics that spread faster, with larger peak incidence, and harder to control [74-77]. In effect these conclusions drove fear among the populace as news media and websites documented hospitalizations and death. Fear can be a motivating factor to promote a health message but can backfire at times [78]. An important consistent conclusion drawn by various studies was the suggestion that a key feature of SARS-CoV-2 infection is the potential for pre-symptomatic transmission. That fueled ideas that vaccination was key to inhibit the spread of the virus since asymptomatic spread was a great possibility [79]. Hence, one can understand the rationale for the emergence of vaccine mandates and terminology around viral transmission.

Variants were often presented in the media as viral waves. The genomic diversity of SARS-CoV-2 provides a lineage map starting from Janus but the media and global health organizations focused on Alpha and Delta [80]. We are presently in the Omicron wave with some countries reporting that the population of individuals with symptomatic COVID-19 is increasing despite having high vaccination and natural immunity rates. As of July 02, 2024, the CDC estimated that COVID-19 infections are growing or likely growing in 39 states and territories, declining or likely declining in 0 states and territories, and are stable or uncertain in 10 states and territories. This alone suggests that despite vaccination and counting those that have experienced natural active immunity through infection, the disease will not be irradicated.

Yet, the tone of scientific manuscripts provides another aspect of confusing messaging which social and news media might pick up. On the one hand, analysis of the genomic lineages suggests that while the early waves of Alpha and Delta relied on increased transmission of the virus, Omicron added viral escape as a driver. The Omicron interacts less efficiently with neutralizing convalescent monoclonal antibody(s) [81]. Review and meta-analysis of the emerging Omicron variant and its lineages concludes they produced "a rapid and significant increase in COVID-19 cases globally while adversely impacting the protective efficacies of existing vaccines and antibodies-based therapies" [82]. In contrast, Wassenar et al suggested that "that a fourth wave of the pandemic with the Omicron variant might not be that different from other VoCs, (variant of concern) and that we may already have the tools in hand to effectively deal with this new VoC" [80]. Early on there was suspicion that viral escape of neutralizing antibodies by SPIKE protein variants was going to be problematic [83]. Targeting the SPIKE protein and not viral core elements can be a mechanism with the result of a limited immune response [84]. However, Antigen Sin is also plausible [85-87]. Should we then be surprised and disappointed that even after vaccination individuals can be infected by Coronavirus variants?

On the one hand, vaccination saves lives. The elderly are a top priority for getting COVID-19 vaccines because data show that their morbidity and mortality are significantly higher than in the younger age group [88-90]. It's invariably more constructive when public health messages target those people who stand the most to gain from preventive measures. To illustrate, a COVID-19 booster campaign focused on the most at risk from the virus is a preferable strategy for today. The CDC found that in 2023 adults over 65 made up almost two-thirds of people hospitalized with COVID-19 and 90% of deaths, but fewer than 25% were up to date on the recommended vaccines (https://www.cdc.gov/mmwr/volumes/72/wr/mm7240a3.htm?s_cid=mm7240a3_w).

Advertisements promoting the benefits of vaccines and boosters using older spokespeople to those for whom there is proportionately far more benefit can be useful especially in venues of trust [91]. It is documented that older folks can find it difficult to focus on deep, in-the-moment listening during conversations [92]. This can be frustrating and may lead to misunderstandings and miscommunications. Aging individuals can be become consumed in thinking, obsessing, and focusing on those memories and events that words trigger, that we end up not listening to what is being said or the new context being built.

On the other hand, systems vaccinology/immunology would suggest that we are all different in how we respond to a virus and to vaccinations [93-95]. There is a long-standing recognized challenge in the vaccination of the "elderly" as T and B cells age with decreased immune function or immunosenescence [96]. The quality of T-cell responses is crucial for determining the disease outcome to various infections [97]. For example, per CDC guidance for live attenuated influenza vaccine in the U.S. for seasonal and pandemic influenza is <49 years of age [98]. Monitoring immune responses globally, it was noted early on that antibody responses to vaccines are lower in the elderly and in those who have comorbidities [99,100].

We have learned from innate immunity to viruses that pattern recognition is fundamental for adequate immunity [101], however, even previously infected individuals are getting symptomatic COVID-19. Being exposed and generating a natural or acquired response to a variant of SARS-CoV-2 is not enough as some individuals are infected multiple times. While protection against severe disease is evident, especially among those with natural immunity, how long this protection lasts is an open question. Perhaps we have entered a time where we will learn to coexist with the virus being satisfied that the merits of vaccination and natural immunity is to limit severe illness and hospitalization and not preventing virus transmission [102].

Lesson 3 – Protection for Others

The goal of vaccine campaigns is two-fold. Protect the one receiving the vaccine and thereby protecting those around the vaccinee. In this way campaigns are assumed to have a herd or community effect. The early concept for herd or community immunity arose with smallpox vaccination -referred to as ring vaccination – immunizing those in close contact with an individual with smallpox. For many common respiratory viruses such as influenza and respiratory syncytial virus, the barriers to achieving herd or community immunity are even greater than with measles, polio, and smallpox. These barriers include asymptomatic transmission, incomplete or short-duration protective immunity, and viral immune escape, all of which displayed in COVID-19 [103]. Indeed, for many respiratory viruses, including SARS-CoV-2, immunity is itself a fluid concept, ranging from complete and relatively durable (long-lasting) immunity that fully protects against infections, to immunity that protects against severe disease but does not prevent reinfection and therefore onward transmission. It is perhaps the latter topic area that perplexes policymakers the most since guidelines for quarantining and mask requirements reflect a perceived "transmissible viral load". If one tests positive for COVID-19 how many days of self-isolation are required to prevent exposing others [104]? Does wearing masks prevent being infected or prevent the spread of the virus [105]? So why was there a discussion of herd immunity or community immunity for COVID-19?

When the initial vaccines were rolling out the U.S. already had about 300K deaths, with thousands more being identified and hospitalized every day. The conclusion was that the virus was spiraling out of control. Public messaging focused on what one can do to minimize individual risk as to reduce the spread of the virus. Various analyses suggested that non-pharmaceutical interventions (including border restrictions, quarantine and isolation, distancing, and changes in population behavior) were associated with reduced transmission of COVID-19 [106,107]. However, at that time since it was not clear what the viral dosing or exposure levels to be achieved for infection for example required for defining safe distancing. Hence, precaution was exercised to attempt to thwart transmission. Perhaps due to perceived urgency to get the virus under control a public message to get as many people vaccinated as possible became a mandate. Hence, the concept of protecting yourself and those around you led the charge. But the changing of opinions leads to communication breakdowns and accusations of lying to the public, fueling mistrust (https://www.statnews.com/2022/03/25/how-we-got-herd-immunity-wrong/) .

At present, the U.S. CDC estimates that about 77.1% of the total U.S. population have received at least one dose of Covid vaccines. About 65.6% of the total population is fully vaccinated with either two doses of the Pfizer or Moderna vaccine or one dose of the Johnson & Johnson vaccine. At the start of the pandemic, figures like 60 to 70% were given as estimates of how much of the population would need immunity from the coronavirus to reach herd immunity. Anthony Fauci in Dec of 2020 stated in an interview with Dana Bash of CNN that he was changing his herd immunity estimates to range between

75-85% based upon Measles compliance vaccination estimates. But measles virus doesn't mutate in a comparable way to SARS-CoV-2 [108] and compliance for herd immunity for Measles is 95%. Muñoz-Alía et al [108], indicated that for Measles virus to escape immunity, the virus would need to generate a large set of mutations — simultaneously — affecting multiple parts of the surface proteins. The authors concluded that there was a near-zero probability for the natural emergence of a new measles virus capable of evading vaccine-induced immunity.

In contrast, SARS-CoV-2, mutated into new strains in its first year as a human disease-causing virus with differing infectious rates. In this context, SARS-COV-2 was more like influenza, which was suggested in 2016 that herd immunity cannot be achieved for the influenza virus [109]. Fauci and colleagues came around to this viewpoint in 2022 [71], while some suggestions were made in 2021 that herd or community immunity would not be achieved for COVID-19 [110]. Fauci correctly made a distinction in the concept of achieving herd immunity via vaccination versus acquired immunity through infection which was deemed dangerous. But headlines didn't message this duality saying only that Fauci and Government Health officials are for it at first, then against it, then for it, then not achieving but perhaps still. Unfortunately, the messaging damage was laid out. A survey of 1476 adults in the UK revealed that COVID-19 vaccine hesitancy is driven by a misunderstanding of herd immunity as providing protection in addition to other factors [111-113].

Lesson 4 – Infection versus Vaccination

Individuals who have survived a smallpox infection are observed to have comparable levels of immunity to those vaccinated with vaccina virus [114]. This is a minimal goal of any vaccine but with the expectation that vaccines create more effective and longer-lasting immunity than natural immunity. Natural and vaccine-induced immunity are observed to be equivalent for the protection against SARS-CoV-2 infection [115,116]. These studies suggest that unvaccinated COVID-recovered individuals should be considered to have at least equal protection to their vaccinated COVID-naïve counterparts. Some reports suggested that natural immunity can be longer lasting [117,118]. However, policy makers thought at the time that natural immunity was not very effective to protect (https://www.washingtonpost.com/outlook/2021/09/15/natural-immunity-vaccine-mandate/) . What's further ironic is that the vaccine manufactures used comparison with natural immunity levels to show that their vaccines were as robust in their immune response as those infected and cleared.

Yet, there emerged a push back against the acceptance of natural immunity despite evidence that natural immunity can be as effective as vaccination [27]. The CDC director was noted to wax and wane on natural immunity and its role in protection while in Europe previous infection was noted in their vaccination passports. Hence the politics of natural immunity and the politics of vaccination emerged. For the public, this all contributes to mistrust as news outlets and social media commented on all the mandates and the back and forth. A call to consider natural immunity in policy making has been made [119]. But unlike smallpox, natural immunity and vaccination against SARS-CoV-2 is short lived. Those who survived active smallpox infections in their youth retained vaccinia-specific immunity throughout their lives and their anti-vaccinia antibody titers were like the levels of vaccinated subjects. Thus, vaccinated subjects remain immune to vaccinia indefinitely and do not require booster vaccinations even if they are many decades removed from primary vaccination.

We are coming to view that the SARS-CoV-2 virus is endemic. The endemic nature of the virus affects both public policy and practical strategies. Among the practical strategies' can endemic human Coronavirus's be a COVID-19 vaccine approach? A hybrid of natural immune response and acquired immunity to SARS-CoV-2 might have been overlooked [120]. This study showed that hybrid immunity from both a fourth vaccination dose and previous COVID-19 illnesses may offer protection against developing long COVID, or post-COVID condition (PCC) [120]. The study is based on 109,707 participant surveys collected about health history and self-reported post-infection symptoms in the German National Cohort. More than 80% of the participants had received three or more COVID-19 vaccinations. Of the 60% of participants who said they had had a previous COVID-19 infection, 35% reported persistent symptoms 4 to 12 months after infection. Of those, 23% reported high PCC, which means nine or more symptoms. Virus variant type had the greatest influence on developing long COVID.

The risk of developing any PCC after a second infection if PCC did not follow a first infection was substantially lower compared to after the first infection, resulting in a long-term risk reduction of around 50%, the authors said. But the risk of developing long COVID was higher in people who were infected less than 3 months following a vaccination, but approximately 50% compared to those who were infected 4 to 6 months after vaccination. Their findings indicate that the risk of developing PCC was strongly reduced for the second SARS-CoV-2 infection, if the first infection did not result in PCC. The authors concluded. "It is possible that the occurrence of breakthrough infections shortly after vaccination is linked to a specific vulnerability of the individual towards PCC, and the apparent protection actually results from confounding" [120].

The endemic nature of the virus might suggest we no longer indiscriminately self-test for COVID to determine if we have contracted COVID. There are statistical guidelines as to when testing should commence using home kits and how long should one quarantine and when to start ant-viral drugs. From a policy perspective it is easy to think that transmission would be thwarted when enough symptomatic individuals complied with home confinement at symptom onset. There is some research on the effect of voluntary self-isolation and distancing on viral outbreak control in the absence of viral treatment [121,122]. A conclusion reached is that the effect of voluntary self-isolation decreases substantially with the proportion of asymptomatic infections increasing. It is widely believed that asymptomatic infections are one of the major sources of influenza transmission, which most likely applies to transmission. A conclusion of such studies is that with a rise in the frequency of asymptomatic infections, the effectiveness of voluntary self-isolation will become very limited requiring other ideas and strategies to be evaluated to contain onward transmission.

Evidence over the last two years draws attention to the fact that asymptomatic infection, short post-vaccinal post-infection immunity, and the mode of transmission of the SARS-CoV-2 variants preclude successful eradication and the virus which will continue to circulate like the flu virus. Consequently, the hunt for pan-coronavirus vaccines, nasal vaccines and rapid manufacturing technologies for variant specific vaccines will continue [123]. Since vaccinating every three months is not feasible, a yearly boost like that for the flu is reasonable. The world has learned to manage and live and with the flu, albeit it is estimated that 12-60K people die yearly from flu complications. We can learn to live with SARS-CoV-2, but like the flu, for some, there will be a cost. This is a justified conclusion, supported with published data and is shaping as the prevailing concept underlying the strategies for managing this infection in the future. Therefore, it is worth putting it on the table for in depth discussion for the brainstorming the better management of COVID.

It would be interesting to have models considering the comparison between the genetic variability of SARS-Cov-2 and the flu virus to predict the coronavirus capacity to continue to present new variants and even new strains at the rate the flu virus does. What would the consequences of a lower variability be? Would the coming variants exhaust their options for escape? In this respect, keeping the intensity of the waves of the pandemic low, especially restricting its access to immunocompromised patients, will greatly reduce the rate of occurrence of new variants. Maybe it is worth discussing once again the necessity of better antivirals for the treatment of COVID (even mild) because this would further decrease the probability of mutation. The models should quantify the probability of this scenario which would diverge from that of the flu in the long run.

Lesson 5- Public Will

The emergence of the COVID-19 pandemic facilitated a desire to understand what we were dealing with [124]. The emergence of variants left us scrambling as to ascertain virulence and impact. The primary objective of global governments was to limit the human and economic impact of the COVID-19 pandemic. Initially the main thrust of activity was NPIs including lockdown measures, travel restrictions and face mask mandates [125]. It was noted such measures can have large societal impacts and they need to be appropriately justified to the population [125]. But very few governments explicitly defined an overall policy goal for coronavirus control. In the US, phrases like 'flattening the curve' and 'protecting health services from being overwhelmed' were intensively discussed and adopted as concepts. Numerous harsh critiques of the failure of US policy goals are in the literature [126-129]. But still messaging is off in that the pandemic will be ended (https://www.state.gov/covid-19-recovery/).

Ironically, the CDC is now advising to treat COVID infections like the flu or any other respiratory illness—even though the coronavirus is nothing like the flu or other common respiratory viruses. This messaging provides a tone that downplays the virus and basically says deal with it. This tone parrots those of then President Trump in 2020 and 2021 which caused an uproar with Fauci and the media. Again, emphasizing the politics of this disease. So has the pandemic ended or are we learning to live with it. This present position emphasizes that it was neither feasible to eliminate the disease nor to continuously ignore it. Our vaccine approach helps reduce mortality and morbidity, but it wanes very quickly. During the pandemic, we've had to accept that vaccination and natural infection is not an infection control strategy. It's a harm reduction strategy. The WHO has ended their public health emergency messaging for COVID and have announced that it has entered an endemic phase, which means that the virus will continue to circulate indefinitely. All pandemics end eventually either fizzling out or until we all agree that enough is enough and act. The real question, then, is how much COVID illness and death are we willing to accept? Hence the public will!!!!

An emerging understanding is that vaccines alone cannot offer the miracle solution many scientists, health officials, policymakers and governments had hoped for in decreasing the number of infections or cases. Although most countries continue to act without a clear definition of an overarching policy goal – instead re-imposing NPI policies to reduce risk – there is now seemingly increased recognition that we will have to 'to live with the virus' one way or another [130]. The rationale for such an advice is changes in the circulating variants and the disease. Although not harmless, COVID is much less of a threat, especially to those vaccinated and/or previously infected. This, actually, is in line with a certain evolutionary strategy to reduce the harm to the host with simultaneously reducing the replication speed and the maximal viral load as well as initiating a long process of a coevolution between the virus and the host [131-133]. How far along that path SARS-CoV-2 can evolve is not clear especially since this strategy is characteristic of DNA viruses.

There are multiple lessons from the pandemic to think about for the future [134]. Public policies globally were inconsistent regarding having or not implementing mandates [134]. Self-regulating activities morphed into mandates both locally and nationally. What remains unclear and highly elusive are articulated long-term strategies for 'living with the virus', which can be effective and efficient, without causing the massive disruption and social harms associated with current coronavirus policies. Their utility or even moral appropriateness depends heavily on the biology of the virus (as noted above) and is prone to change during the pandemic. In the context of widespread mistrust, the necessity of changing course, adapting to the changing circumstances is misinterpreted as indecision, fueling further mistrust. Toward that end, it is crucial to consider basic immune system functions, and secondly, to better factor the known specific immunological pathways of SARS-CoV-2. Going forward, the U.S. and maybe all countries must carry out the difficult work of adopting strategies that support sound public health measures while countering population mistrust. In this context, officials will have to strike a delicate balance (https://theconversation.com/why-using-fear-to-promote-covid-19-vaccination-and-mask-wearing-could-backfire-153865).

What is interesting is that those that mistrust and hence not willing to be vaccinated etc. are labeled as science deniers yet the messaging from the science community is not as straight forward as thought. A key role in the erosion of rational thinking and confidence in science was played by social media [135-137]. Public opinion is shaped in significant part by social media [138]. The new circumstances of widespread horizontal communication provide advantages in disseminating information but no guarantees for its quality. However, it is evident that in the present era a community-engagement strategy to boost vaccine confidence is necessary as opposed to Government structured vertical communication. Trying to increase public understanding, which is a traditional approach, has been met with resistance by many of the public who understand scientific facts but disagree with findings or uncomfortable with presumed implications. Thus, education alone may be insufficient. It has been recommended that efforts going forward focus on building the 'trustworthiness' of science and Government entities, an approach that will require a paradigm shift away from a focus on correcting individual beliefs and knowledge, to acknowledging and addressing the root causes underlying mistrust [72]. Building trust in science will require including people from communities as equal partners (horizontal communication) from the start of policy discussions. It will certainly necessitate also addressing the wider problem of the emergent social pathology [139].

Conclusion

So, what does the future hold [134]? While 81% of the U.S. population has received at least one dose of COVID-19 vaccine two concepts emerge. The first concerns Community immunity. This was always considered the greatest asset for protecting vulnerable individuals. Herd or community immunity became defined as a percentage of the population that needed to be immunized to stop transmission. The estimates of this percentage were continuously updated as we learned better the epidemiology of COVID-19 and with the changes of the virus itself. Due to the social pathology causing de-rationalization, public thinking failed to keep up with the complexity of the situation which contributed to mistrust among the populace.

The perceived mixed messaging on herd immunity along with changing policies resulted in questioning of scientific recommendations which can impact on acceptance, eroding trust in the medical establishment. Secondly, politicization of science, including those among members of the medical community, is formidable. Framing scientific uncertainty of dealing with the pandemic without policy paralysis is a challenge, but the rhetoric from either end of the policy-making spectrum can cause messaging chaos. The extreme political polarization in which the narrative on each end of the spectrum is progressively de-rationalized is one of the key symptoms of the social pathology discussed here. Among authors a consensus emerges that public health expertise cannot always handle emerging health hazards in a way that provides clear messaging [18,20,137]. This of course provides leeway to political concerns to affect public policies. Political aims run the risk of becoming closely connected to the ability to speak in the name of science. Yet when there is scientific uncertainty the confidence in the authorities, including political, becomes crucial. What should we do if the social pathology has brought it to a new low?

COVID-19 stoked uncertainty and fear. Infection is now happening all the time but without burdening our healthcare system. Hence the shift from pandemic to endemic. So how does one handle an endemic vial illness? According to the U.S. CDC one should act the same way they act when trying not to spread flu or other respiratory diseases. So perhaps the messaging associated with flu vaccination might spillover to those needing COVID-19 immunization [140]. Ultimately, our strategies necessarily adapt coevolving with the virus and the changing mechanisms of the epidemic.

Conflict of /interest

None noted

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