A review of leading COVID-19 vaccines, the quest for immune protection, and its key challenges

Part 3: Covid-19 vaccines – Key challenges and translational science

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Summary

Rationale

• Developing and deploying safe and effective COVID-19 vaccines are faced with many challenges and unanswered questions.

• Massive amounts of heterogenic scientific data are being generated that are needed rapidly to advance vaccine development, protect people and restore normality.

• The purpose of Part 3 of this four-part series is to review the scientific considerations related to key challenges associated with COVID-19 vaccines and immune protection with the focus of making this data more meaningful and open for clinicians.

Key points

• The primary immunogen (antigen) required to induce neutralising antibodies (humoral) and T cell (cellular) immune responses is the S-protein fragment of SARS-CoV-2.

• Currently, the evidence is firmly pointing towards neutralising antibodies, being more critical for protection.

• Long-term protective or durable immune memory is driven by virus-specific T cell and B cell responses (adaptive immunity).

• Circulating antibody titres are not predictive of T cell immune memory.

• Durable immune memory is a crucial factor to sustain herd immunity.

• Adjuvants are added to certain vaccines to provoke a more robust and durable immune response.

• Adjuvants that provoke TH1-biased immune responses are preferred.

• 90% of adults are seropositive for 'common cold' CoV strains.

• There is a cross-reactivity between specific T cell of SARS-CoV-2 and 'common cold' CoV's.

• Prior infection with 'common cold' can play a potentially protective role.

• Seropositive individuals present with a rapid and higher antibody immune response after a single dose with an mRNA vaccine.

• Vaccine-induced immune responses resulting in non-neutralising antibodies, low antibody titres, and abnormal T cell responses (TH2- biased) are potential risks for serious enhanced disease events but unlikely events.

• Vaccine strategies aimed at inducing high titres on neutralising antibodies and TH1-biased immune responses reduce the risk of serious adverse events.

• Emerging variants of concern are extremely infectious, highly transmissible and threatens the protective efficacy of current vaccines.

Public health implications

• A rapid global vaccination campaign combined with standard mitigation measures to stop transmission is the best defence against the emergence of further SARS-CoV-2 variants and the safest way to attain herd immunity.

• Booster immunisations may be required to promote or improve the durability and strength of vaccine immunity.

Introduction

The COVID-19 pandemic is an unprecedented global crisis that has been met by a rapid and remarkable governmental, institutional, scientific, technological and administrative response. Since COVID-19 was declared a pandemic in March 2019, scientists from academic institutions and organisations worldwide have published numerous research studies and clinical trials on diagnosis, prevention, therapeutic strategies, and vaccines – all of which are critical to the worlds ability to return to normality.[1] Prioritising leading vaccine candidates and moving them as fast as possible through clinical trial stages safely and efficiently is urgently needed due to the limited amount of resources available and to control the COVID-19 pandemic effectively .1

Developing, manufacturing, testing and getting a vaccine to people in the community is a long and challenging process. During public health emergencies, such as the COVID-19 pandemic, translational science is an effective tool to turn observations into therapies, including vaccines.[2] Translational science is defined as "the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and populations." [2] This applies to medical procedures, diagnostics, behavioural interventions and vaccines.[2] Its focus is to cut through the operational roadblocks to contribute to new knowledge and understanding about pathogens such as SARS-CoV-2, COVID-19 disease, and the development of vaccines to prevent infection.

Large amounts of data are being generated that are needed rapidly to advance vaccine development and deployment. However, the data is so large to share and to manage and are so heterogenic due to various platforms that are being used combined with diverse target populations that it cannot be combined easily for interpretation and understanding. The focus of translational science to make research data on SARS-CoV-2 and COVID19 more meaningful, open, and accessible for scientists and clinicians.2

Purpose

The purpose of this 4-part series is to enhance private and public health care practitioners, as well as policymakers, knowledge and understanding of the what, why, and how COVID-19 vaccines are emerging, their key challenges and their impact on immune protection against COVID-19.

Part 1 explores the emerging leading COVID-19 vaccine landscape, vaccine platforms and the current status of global COVID-19 vaccination campaigns.

Part 2 provides an overview and summarises the evidence-based research from relevant interim published results from phase 1/2/3 clinical trials supporting the tolerability, safety and efficacy of current leading vaccines approved for emergency use.

Part 3 investigates the scientific considerations related to key challenges associated with COVID-19 vaccines and immune protection.

Part 4 highlights the logistical and ethical challenges of the supply and distribution chain of COVID-19 vaccines.

Literature search methodology

The emerging literature on COVID-19 vaccines is scattered over various sources, characterised by lack of, or incomplete or uncontested evidence-based data and by a plurality of voices within the health care, academic, research, and pharmaceutical, community as well as health care, regulatory and governmental organisations. The pandemic and emerging SARS-CoV-2 variants and their implications are rapidly evolving, making it difficult to clearly and rapidly synthesise and articulate scientific evidence. There is a need for timely and accurate evidence to inform and update private and public health care practitioners and policy decision-makers on the developing status of COVID-19 vaccines.

A comprehensive literature search of multiple bibliographic databases was conducted, including Medline, Embase, the Cochrane Collaboration and Google Scholar. COVID-19 repositories with lists of grey literature sources (e.g., LitCOVID, COVID-END and WHO-COVID-19) and preprint servers or repositories for biological and medical sciences (e.g., medRxiv, bioRxiv) were also included in the search strategy. Preprints are initial reports of research work that has not been peer-reviewed yet. Information derived from preprints thus has to be interpreted with caution. Studies and reviews in all languages were considered for inclusion. Search keywords used in this review include COVID-19, coronavirus, SARS-CoV-2, vaccines, immunogen, immune memory, immune protection, adjuvants, seropositive, vaccine-induced disease, SARS-CoV-2 variant, mutations, antigenic drift, immune escape, vaccination serious adverse events, neutralising antibodies, vaccination, herd immunity. Electronic databases were searched to March 31, 2021.

What is the key immunogen for COVID-19 vaccines?

The development of vaccines is one of the most important medical interventions in infectious disease prevention.[3] Generating protective T cell and B cell immune responses is a critical element of vaccine development.[4] SARS-CoV-2 is a single-stranded RNA virus that replicates in the cytoplasm and consists of four structural proteins: spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein.5 The S-protein plays a critical role in inducing immune responses.[6]

The S-protein, displayed on the virus surface, allows SARS-CoV-2 to enter host cells via the angiotensin-converting enzyme 2 (ACE2) receptor.[7,8,9] The S-protein consist of two subunits, S1 and S2. The S1 subunit contains a fragment called the receptor-binding domain (RBD) that can bind to the ACE2 receptor on the host cell, whilst the S2 subunit mediates membrane fusion.[10,11,12]

Delivering a conformationally correct and stable protein is a crucial requirement for a vaccine to induce an immune response.[13] The S-protein is a dynamic protein that presents itself in a prefusion or postfusion conformational state. Displaying S-protein's original surface contours and chemistry in its original prefusion conformational state will preserve the antigen epitopes necessary for eliciting a strong neutralising antibody response.[13] The research done by Pallesen and co-workers [14] on stabilising the S-protein of MERS-CoV has provided knowledge to manipulate the S-protein in its prefusion stabilised form. It has provided the basis of COVID-19 vaccine development.[15]

The S-protein gene in the viral genome is therefore considered as the key target for COVID-19 vaccines.[16] The S1 subunit fragment of the S-protein fragment, also referred to as the RBD, is considered as the key immunogen (antigen) that can induce humoral (neutralising antibodies) and cellular (T cell and B-cell) immune responses.[17,18,19]

Will vaccine induce long-term immune memory and protection?

Immune memory against the SARS-CoV-2 S-protein is essential to ensure protection against reinfection and vaccine efficacy. Immune memory compartments for COVID-19 disease consist of SARS-CoV-2 specific circulating neutralising antibodies, memory CD8+ T cells, memory CD4+ T cells, and memory B cells. SARS-CoV-2 specific CD4+ T cells and CD8+ T cells are associated with reduced COVID-19 disease severity,[20] whilst rapid production of neutralising antibodies was associated with a significant reduction of viral load after infection over 14 days.[21] Dan and co-workers22 suggest that both abovementioned associations are consistent with the hypothesis that the observed immune responses would be capable of substantially limiting SARS-CoV-2 transmission, resulting in reduced COVID-19 incidence, disease severity, hospitalisations and deaths. Current evidence suggests that only SARS-CoV-2 specific neutralising antibodies can provide sterilising immunity.[22]

Reports that serum levels of SARS-CoV-2 specific neutralising antibodies decrease after recovery from COVID-19 infection have raised a lack of durable immunity. However, the absence of SARS-CoV-2 specific neutralising antibodies does not necessarily indicate an absence of immune memory.[22,23] SARS-CoV-2 infection also activates innate immunity and dendritic cells that drive the induction of virus-specific memory B- and T cell immune responses (adaptive immunity), suggesting antiviral immunity.[23,24]

Longitudinal assessment of individuals recovered from mild COVID-19 showed that virus-specific neutralising antibodies could persist for at least three months in most

subjects.[24] In another study, it was concluded that substantial immune memory was retained in about 95% of individuals involving all four major types of immune memory ~6 months after infection.[22] Neutralising antibodies against SARS-CoV-2 S-protein moderately declined over eight months. S-protein IgA was still present in most subjects at 6-8 months after infection.22 SARS-CoV-2 S-protein specific memory B-cells increased between 1-8 months after infection, whilst memory CD8+ T-cells and memory CD4+ T-cells declined with an initial half-life of 3-5 months22. SARS-CoV-2 specific memory CD4+ T-cells that drive B-cells, also referred to as T follicular helper (TFH) cells, were also highly preserved at 6-8 months. [22]

The mechanisms of protective immunity against SARS-CoV-2 or COVID-19 are not defined in humans yet. Therefore, direct conclusions about protective immunity cannot be made based on quantifying any of the immune memory compartments.[22] However, data suggests that neutralising antibodies are adequate to protect against infection and improve disease outcome.[15]

Currently, the evidence is firmly pointing towards neutralising antibodies, being more critical for immune protection. The common assumption made by the research community is that vaccine immunity will wane and that booster immunisations might be needed if the virus is still circulating.[15] Durable immune memory irrespectively of whether the infection is in the context of naturally acquired or vaccine-induced, is essential for the prevention of COVID-19 at the population level and to sustain herd immunity.[25]

What is the role of adjuvants in vaccines?

Adjuvants are essential chemical ingredients added to certain vaccines (e.g. protein subunit- and inactivated virus-based vaccines) to provoke more robust and long-lasting immune responses.[26] Adjuvants induce unique profiles about strength, direction, and duration of neutralising antibodies (humoral immune response),[26,27,28] or modulate cellular immune responses by influencing T cell-derived cytokine patterns.[13]

Aluminium salts (Alum) was the first adjuvant used in licenced human vaccines and formulated in many other vaccines[29,30] are most widely used due to their ability to strengthen immune responses and have an excellent safety track record.[26] Alum adjuvants have therefore been prioritised for use in exploratory and preclinical studies.[29,30] Although Alum has been formulated with S-protein or RBD to boost production of neutralising antibodies,[29,30,31] it cannot boost T cell-mediated immune responses (CD4+ and CD8+ cells).[20]

Recent studies have suggested that Matrix M, a saponin-based adjuvant, is more effective than Alum at boosting more robust neutralising antibodies to SARS or MERS S-protein.[32] It is suggested Matrix M adjuvant may prevent serious adverse events such as antibody-dependent enhancement (ADE), which is more likely to be provoked by weak antibody production or too much antigen (S-protein).[33] Matrix M adjuvant is

combined with the S-protein antigen in protein subunit-based vaccines (e.g. (Novavax),[34] with the purpose to boost neutralising antibodies, reduces the amount of antigen needed, and direct the immune response towards a T-helper (TH1) antibody response.[15,26] CD4+ T cells, traditionally known as T-helper cells (TH), are critical elements in promoting specific cell-mediated immune response to fight viral infections.35 TH cells stimulate B cells to produce neutralising antibodies, cytotoxic T-cell activity to eliminate virus-infected cells and enhance immune memory.[35] The TH1 CD4+ T cell subset are critical for antiviral responses, whereas the TH2 subset of CD4+ are mainly linked with the production of antibodies, and anti-helminth infections.[35]

It is suggested that adjuvants (e.g. Matrix M) known to direct TH1 immune response are superior compared to those adjuvants (e.g. Alum) that direct the response toward TH2 immune response should be cautiously evaluated.[15,26] Until all the adjuvant formulations are tested, it remains unknown which formulation will provide a safer and more efficacious vaccine.[26]

What is the potential impact of 'common cold' Coronavirus (Cov) on SARS-CoV-2 infection or vaccination?

There are seven Coronavirus (CoV) serotypes, four associated with the 'common cold' (229E, HKU1,OC43, and NL63), and MERS-CoV, SARS-CoV-1, and SARS-CoV-2 that is associated with highly infectious disease. [36] Seropositivity for the 'common cold' coronavirus strains in adults is estimated at 90%.[37] Scientific literature suggests that prior infection with common cold CoVs could induce cross-reactivity between 'common cold' antibodies and the S-protein antigen of SARS-CoV-2, thus providing a protective effect.[38]

Viral vector-based vaccines present with two challenges, namely pre-existing immunity to the viral vector and the SARS-CoV-2.15 Recent studies show that ~40-60% per cent of healthy SARS-CoV-2 seronegative individuals present with memory CD4+ T cells that recognise SARS-CoV-2 antigen, suggesting a cross-reactive T cell recognition between SARS-CoV-2 and common cold COVs.[39,40,41,42,43,44] These findings indicate that viral vector-based vaccines may boost pre-existing cross-reactive memory CD4+ T-cells in some individuals, thus providing a potential mechanism for differential susceptibility to SARS-CoV-2 infection. [41,42,43,44] It was also noted that 52,4% of participants receiving the CanSino vector-based vaccine had high pre-existing immunity to the Ad5 viral vector used in this vaccine. Significant weaker immune responses to the vaccine were observed in the elderly.[45] This finding suggests that the Ad5 viral vector-based vaccine may be less effective in the elderly.[45]

To date, there is no direct evidence indicating that pre-existing immunity to common cold COVs may be harmful to the outcome of SARS-CoV-2 infection or negatively affect vaccination.[36]

How will seropositive individuals react after a single dose of vaccine?

A recently published study noted that seropositive individuals presented with a rapid antibody response after receiving a single dose of an mRNA vaccine (Pfizer-BioNTech or Moderna).[46]

Individuals who previously had COVID-19 (seropositive), followed up two weeks after a single dose of mRNA vaccine, had antibody concentrations ten-fold higher than those observed in uninfected individuals (seronegative) that received two doses of the vaccine. [46,47] A study of a cohort of health care workers recently published also confirmed that antibodies in seropositive individuals might boost the first dose.[48] This suggests that PCR confirmed seropositive individuals might potentially only require one dose of an mRNA vaccine, especially in cases where vaccine supplies are limited.[46,47] However, incorporating one dose of mRNA vaccine into a vaccine campaign may be a logistically complicated process. Therefore, it may be easier and safer from a logistical perspective to apply a two-dose regimen.

Further research is required into the effect of prior infection to SARS-CoV-2 on the magnitude and durability of vaccination immune responses.[48]

How likely is the possibility that COVID-19 vaccines will elicit serious side effects

Although unusual and unlikely, vaccine-induced events that enhance SARS-CoV-2 infection or COVID-19 disease can occur and are potential risks when giving vaccines to otherwise healthy people.[49]

- **Antibody-dependent enhancement (ADE)**

SARS-CoV-2 neutralising antibodies are currently at the epicentre of all COVID-19 diagnostics, treatments and vaccine endeavours to control the COVID-19 pandemic. Neutralising antibodies (nAbs) are the main objective of COVID-19 vaccines. nAbs bind to the target antigen, the tip of the S-protein or RBD that binds to the ACE receptor and shuts its function down.

COVID-19 disease can potentially be enhanced by SARS-CoV-2 non-neutralising antibodies through antibody-dependent enhancement.[50] Thus, raising non-neutralising antibodies that do not protect are also blamed for worsening the condition through ADE.[51] Repeated exposed to seasonal 'common cold' CoV's produce CoV specific antibodies that can cross-react with SARS-CoV-2 specific antigens[52] to produce non-neutralising antibodies that increase the viral entry of host cell[36], increased viral infectivity[50] and increased disease severity.[53,54,55,56] Current evidence suggest that elder individuals may be more susceptive to ADE.51 ADE is also more likely to occur when a vaccine produces antibodies with inadequate specificity and mild antibody concentration[33] or non-neutralising antibodies.[13]

It is suggested that full-length S-protein instead for fragments is more likely to produce reduced levels of antibodies that could potentially trigger ADE,[33] manifested by severe liver damage and enhanced infection.[57] In contrast, high affinity neutralising antibodies could help to avoid ADE.[26] Other solutions suggested to inhibit ADE is to increase the dose of antibodies and to use protease inhibitors and Fc inhibitors.[58,59]

Research data suggest that vaccination strategies that focus on high titres of neutralising antibodies have the best chance of success with the least risk of ADE.[50] It is also suggested that protein subunit-based vaccines can elicit increases titres of S-protein specific neutralising antibodies, thus reducing the risk of ADE.[50] Also, the use of adjuvants depends on the choice of antigens used. For example, the N protein is generally highly conserved and can promote pro-inflammatory cytokine production, induce cytotoxic T lymphocytes, resulting in severe lung pathology.[60]

There are no reports of ADE occurring in participants enrolled in vaccine clinical trials,[51] or with any of the variant strains reported worldwide.

- **Vaccine-associated enhanced respiratory disease (VAERD)**

VAERD occurred in young children in the 1960's when whole inactivated virus vaccines against the respiratory syncytial virus (RSV) and measles were tested.[61] This vaccine-induced disease, compounded by the conformation vaccine antigen, is characterised by the generation of excessive non-neutralising antibodies.[13,62] an abnormal T cell immune response accentuated by increased production of T_H2 cytokines (interleukin-4 (IL-4), IL-5, and IL-1), and attenuated cytolytic T cell activity, with resultant allergic (eosinophilic) and airway hyperresponsiveness .[13,36] Allergic inflammation of the airway due to RSV was also noted with using whole inactivated virus vaccines.[63] T_H2-biased CD4+ T cell immune responses associated with RSV and VAERD were also consistent with animal models' findings.[64]

Because vaccine-induced events can potentiate airway dysfunction and delay viral clearance, avoiding T_H2-biased immune responses may be important, especially in young infants with small airways that can be easily obstructed.[13]

Whole-inactivated virus was implicated in almost all cases of where was VAERD demonstrated in human clinical trials for RSV and measles and in animals for SARS.65 However, based on the experience gleaned with other viral infections and viral vaccines, whole inactivated virus vaccines do not have an intrinsic potential to elicit harmful immune responses.[36] None of the current leading vaccines undergoing clinical trials have shown any evidence of immune enhancement of SARS-CoV-2 infection.[36]

Guidelines for COVID-19 vaccine development to reduce the risks of vaccine-enhanced diseases should be informed by prior work on RSV vaccines,[66] including use of conformationally correct antigens to elicit high-quality titres S-specific neutralising antibodies[13], and avoiding induction on non-neutralising antibodies, and T_H2-biased

immune responses.[51,66] Many candidate vaccines (viral vector, mRNA and protein subunit) favour a T_H1 immune response, whereas Alum adjuvanted inactivated viral vaccines could potentially elicit a T_H2 biased immune response.[51]

Inactivated whole virus or viral vector vaccines that have a more significant potential for driving T_H2 biased immune response and causing vaccine-induced immune pathology should be closely monitored in real-time during human safety and efficacy trials. [67,68]

Do new SARS-CoV-2 variants escape neutralising antibodies, and what are the implications for vaccines?

Viruses mutate, so new variants are not surprising. However, the phenotype associated with those changes is a potential cause of concern, particularly if they impact immune memory or vaccine efficacy.[69] A recent study suggested that reinfection by seasonal coronaviruses (OC43, 229E) may be due to adaptive genetic evolution in the region of the viral S-protein, enabling them to escape recognition by the immune system.[69]

Since December 2020, several novel SARS-CoV-2 variants with multiple mutations of S-protein have emerged. Variant VOC 202012/01 (B1.1.7, 501Y.V1) was identified in the United Kingdom[70,71], variant 501Y.V2 (B.1.351, 20H) in South Africa[72], and variant P.1 (501Y.V3. 20J) first identified in Japan and described by Brazilian scientists.[73,74] Variants of SARS-CoV-2 are highly infectious, highly transmissible, are not associated with severe disease, and have now spread to other countries worldwide.[75,76] In recent weeks, US researchers have identified several new variants in the USA. Scientists are currently actively involved in sequencing the SARS-CoV-2 variant genomes to characterise the implications of newly identified variants. The unofficial policy is: "that every variant is a variant of concern until otherwise proven".[77]

The VOC 202012/01 variant has spread globally, exhibiting similar increased transmission rates (59-74%) in Denmark, Switzerland, and the United States.[78] Their rapid transmission and potential for immune escape have raised concerns regarding their potential impact on antibody therapy, vaccine efficacy, and reinfection risk.[76] Variant 501Y.V2 (B.1.351, 20H) contains multiple mutations within two immunodominant domains on the S-protein. It has shown substantial or complete escape from neutralising antibodies from therapeutically relevant monoclonal antibodies in COVID-19 convalescent plasma.[72] In vitro data demonstrate that as much as a ten-fold reduction in neutralising antibodies in vaccinated samples against mutant S-protein pseudovirus.[79,80,81] It has also been noted that point mutations in major histocompatibility complex-I protein viral epitopes of the S-protein enable SARS-CoV-2 to subvert CD8+ T-cell surveillance.[82] New emergent variants with S-protein mutations are a concern and threatens the protective efficacy of current vaccines.

It was shown that variant 501Y.V2 (B.1.351, 20H) is largely resistant to neutralising antibodies induced by initial circulating SARS-CoV-2 lineages.[72] Although the ChAdOx1nCoV-19 (Astrazeneca/ Oxford) vaccine showed high efficacy against the

original coronavirus (non-501Y.V2), early preliminary data that have not yet been subjected to peer review show that the AstraZeneca vaccine has a clinical efficacy of only 22% against the variant 501Y.V2 (B.1.351, 20H), providing minimal protection against mild-moderate COVID-19 infection. Efficacy against severe COVID-19 disease, hospitalisation and deaths was not assessed.[83] The use of this vaccine has subsequently been suspended in South Africa.

Preliminary data show that Novavax, a US-produced vaccine has an efficacy of 86% against the variant VOC 202012/01 (B1.1.7, 501Y.V1) and 60% against the variant (501Y.V2).[84] Moderna reported that in-vitro studies showed that its mRNA vaccine would be effective against the VOC 202012/01 (B1.1.7, 501Y.V1) and 501Y.V2 (B.1.351, 20H) variants. However, the new variant 501Y.V2 (B.1.351, 20H) was associated with a substantial reduction in neutralising antibodies.[76] Pfizer has revealed that its BioNTech mRNA-based vaccine is effective against the VOC 202012/01 (B1.1.7, 501Y.V1) variant. Both Moderna and Pfizer studies have not been subjected to peer review yet and should be interpreted with caution. Both developers are investigating booster shots to protect against variants of SARS-CoV-2.[76]

A recent study conducted in South Africa to test the efficacy of Novavax (NVX-CoV2373) on variant 501Y.V2 (B.1.351, 20H) was found that the vaccine was efficacious in preventing mild to moderate disease.[85] In another recent study with a two-dose regimen with the Oxford/ Astrazeneca vaccine, individuals infected with the 501Y.V2 (B.1.351, 20H) variant had no protection against mild-to-moderate COVID-19 disease.[86]

The VOC 202012/01 (B1.1.7, 501Y.V1) variant is not considered as an immune escape variant, which would pose a major concern for current leading vaccines or risk of SARS-CoV-2 reinfection.[71] Studies noted that the VOC 202012/01 (B1.1.7, 501Y.V1) variant remains sensitive to neutralisation but at moderately reduced levels (~ 2 -fold reduction), suggesting a minimal impact on vaccine efficacy in people who receive both doses of Moderna and Novavax vaccines.[71] Although the VOC 202012/01 (B1.1.7, 501Y.V1) variant is associated with increased viral loads, imparts increased infectivity, and spreads more rapidly, and it does not increase disease.[75]

Wibmer and co-workers have suggested that new antigenically distinct variants remain a concern and pose a significant reinfection risk due to the reduced efficacy of current leading vaccines approved for emergency use.[72] Furthermore, the role of non-neutralising antibodies and the efficacy of T cell responses on 501Y.V2 (B.1.351, 20H) variant, and the correlates of immune protection against infection and severe COVID-19 disease, remains to be elucidated.[72] Also, there is an urgent need for rapidly adapting current vaccine platforms considering the extent and speed of 501Y.V2 (B.1.351, 20H) variant immune escape against neutralising antibodies.[72] It is suggested that if SARS-CoV-2 evolves adaptively in the S1 region, similar to that of seasonal 'common cold' CoV's, then it is possible that SARS-CoV-2 vaccines would need to be frequently adapted to match the novel variant strains, as is done with seasonal influenza vaccines.[69]

According to Altmann and co-workers[87], a rapid global vaccination campaign combined with standard mitigation measures to stop transmission is the best defense against the emergence of further SARS-CoV-2 variants because "a virus that cannot transmit and infect others has no chance to mutate".

Can herd immunity be achieved through vaccination?

Herd immunity at a population level, usually ~60-70 % of the population, can only be derived from continuing natural infection or vaccination. Using vaccines to target specific high-risk populations, such as frontline health care workers, vulnerable people such as the elderly, are particularly suited for attaining herd immunity.[88]

Herd immunity can only be achieved by reducing the transmission chain measured by R (Reproduction number) to below 1.[25, 52] However, many factors can affect herd immunity in the real world situation, including vaccine efficacy, duration of immune memory, waning antibodies52, reinfection with variants[89,90] availability of vaccines, vaccine hesitancy, individual behaviour and kinetics of transmission that is complex and not understood.[15]

Decreasing immunity, vaccine hesitancy, the emergence of new strains, and the inevitability of world travel may increase the incidence of new infections, thus requiring revaccination over several seasons.[91] Thus, achieving herd immunity through vaccination, although an attractive goal, may still be elusive. Therefore, to limit spread and reinfection, mask-wearing, hand washing, and social behaviour remain necessary infection prevention measures that must be adhered to.[92]

Conclusion

The COVID-19 vaccine pathway from development and deployment to immune protection is a long and challenging process facing many challenges and requires massive amounts of diverse data. Scientific data that is needed rapidly to advance our knowledge and understanding of the coronavirus disease is urgently needed to provide immune protection that is not easily accessible and meaningful for clinicians to interpret and understand.

To achieve immune protection, it is critical to generate SARS-CoV-2 specific neutralising antibodies and protective immune memory B cells and T cells. The S-protein fragment also referred to as the RBD of the SARS-CoV-2 virus, must be delivered in a conformationally correct and stabilised form to mediate its function as an immunogen (antigen) and to be able to induce a targeted humoral (neutralising antibodies) and cellular (B- and T cell) immune responses.

Immune memory for COVID-19 disease consists of 4 compartments, neutralising antibodies, memory B cells, memory CD8+ T cells and CD4+ T cells. Current research indicates that significant immune memory is retained in about 95% of individuals involving all four major types of immune memory ~6 months after infection. Currently, the balance of research data points strongly towards neutralising antibodies being more critical for immune protection. At this point, no direct conclusions about protective immunity can be made based on quantifying SARS-CoV-2 circulating antibodies, memory B cells, CD8+ T cells and CD4+ T cells.

The T-helper 1 (TH1) CD4+ T cell subset is critical and preferred for antiviral immune responses, whereas the T-helper 2 (TH2) CD4+ T cell subset is mainly linked to anti-helminth immune responses. Although TH1-biased immune responses are preferred, all adjuvant formulations in candidate vaccine, especially protein subunit and inactivated candidate vaccines, should be rigorously assessed to determine which formulations are superior or inferior.

Cross-reactive T cell recognition between SARS-CoV-2 and 'common cold' CoV's can occur, and pre-existing immunity to 'common cold' CoVs can potentially provide protective immunity against SARS-CoV-2 infection. However, there is no direct evidence suggesting that pre-existing immunity to 'common cold' CoV's is harmful to the outcome of SARS-CoV-2 infection or vaccination.

Although seropositive individuals present with higher antibody responses after the first dose of an mRNA vaccine, further research is required to establish the magnitude and durability of vaccination immune responses in seropositive individuals.

Vaccine-induced immune responses, including low neutralising antibody titres, non-neutralising antibodies, and TH2-biased immune response, are potential risk factors for unusual and rare serious adverse events such as ADE and VAERD. Currently, there are no reports of any antibody disease enhancement in participants enrolled in vaccine clinical trials.

Several new variants with mutations in the S-protein that have emerged recently are a concern for immune escape and threaten current vaccines' protective efficacy due to the virus's ability to escape neutralising antibodies. Considering the speed and scope of immune escape by emerging variants, there is an urgent need for rapidly reformulating current vaccines to counteract circulating strains.

Achieving herd immunity at a population level with vaccines may be difficult to obtain due to vaccines' availability, vaccine hesitancy, waning immunity, the emergence of new strains and seasonal reinfections, and individual behaviour. Therefore, usual mitigation measures such as mask-wearing, hand washing/sanitising and social behaviour remain essential measures that must be adhered to t prevent the spread of SARS-CoV-2 while vaccination campaigns are in progress.

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