MINI-REVIEW

Longevity of vaccine protection: Immunological mechanism, assessment methods, and improving strategy

Zhian Chen1,2  |  Xin Gao2  |  Di Yu1,2

1 The University of Queensland
Diamantina Institute, Faculty of Medicine, The University of Queensland,
Brisbane, Queensland, Australia
2 Department of Immunology and Infectious Disease, John Curtin School of Medical Research, Australian National University, Canberra, Australia

Correspondence
Di Yu, The University of Queensland Diamantina Institute, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia.
Email: di.yu@uq.edu.au

Abstract
Vaccination represents one of the most important achievements in modern medicine. During the era of COVID-19 pandemic, the successful vaccination for SARS-COV-2 is the major hope to bring the society back to normal. However, although vaccines, such as for smallpox and poliomyelitis, can trigger lifelong protection in individuals and help to generate the herd immunity resulting in the eradication of pathogens, other vaccines, with seasonal influenza vaccine as a case in point, are unable to induce sustained immunity so that repeated vaccination is required. As most vaccines were developed empirically, the immunological mechanism underlying the longevity of vaccine-induced protection remains only partially understood. In this review, we first describe vaccine-induced humoral immune response in which long-lived plasma cells and memory B cells are produced. We then summarise methods using immunological correlates of protection to assess the longevity of vaccine efficacy and provide the evidence and knowledge for the duration of protection by current vaccines. Last, we discuss rationale and strategies to improve the duration of vaccine protection by targeting vaccine immunogenicity, antibody affinity, avidity and prime-boost scheme.

KEYWORDS
correlates of protection, immunological memory, plasma cells, vaccine efficacy

Abbreviations: ACIP, The Advisory Committee on Immunization Practices; ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cells; BCG, Bacillus Calmette–Guérin; BCR, B-cell receptor; CD40L, CD40 ligand; CoP, correlates of protection; DCs, dendritic cells; ELISA, enzyme-linked immunosorbent assay; FDC, follicular dendritic cells; GC, germinal centre; HIV, human immunodeficiency virus; HPV, human papillomavirus; IL-21, interleukin-21; LLPCs, long-lived PCs; LPS, lipopolysaccharide; mCoP, mechanistic correlates; MHC, major histocompatibility complex; MPL, monophosphoryl lipid A; nCoP, non-mechanistic correlates; PC, plasma cell; SHM, somatic hypermutation; SLOs, secondary lymphoid organs; T FH, follicular helper T; T H1, type 1 helper T cells, T H2, type 2 helper T cells; TLRs, Toll like receptors; T RM, tissue-resident memory T cell; VLP, virus-like particle

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1 | INTRODUCTION

Vaccination is undoubtedly one of the most successful and cost-effective medical interventions in the history of humankind.[1] Since the 20th century, the implementation of the vaccination programs against various pathogens in large populations has enormously extended the global human life expectancy and saved trillions of dollars in socioeconomic cost. Despite the proven success in controlling and even eliminating infectious diseases, such as smallpox, polio, and tetanus,[2] developing vaccines also shows challenges against many other infectious diseases, such as malaria and human immunodeficiency virus (HIV), reflecting our incomplete knowledge in the immunology underpinning vaccine-conferred protection. Indeed, the majority of available vaccines were designed empirically without accurate understanding of the mechanism of action.[3,4]

The ultimate goal of vaccination is to generate long-lasting immune protection against pathogens. In a very simplified perspective, vaccines represent the harmless mimics of natural pathogens and induce immunological memory, which rapidly mounts robust immune responses upon exposure to “real” pathogens and prevent severe diseases and further transmission.[5] Vaccine-induced immune responses are highly complex and include orchestrated actions of a wide range of immune cells in both innate and adaptive immune systems.[1] The specific protection mechanism varies for different vaccines and leads to distinct longevity of protection. While life-long protections are observed in certain vaccines, such as for smallpox,[4] there is growing evidence suggesting that many other vaccines can lose their effectiveness of protection faster than previously conceived.[6–9] Therefore, the durability of vaccine efficacy is often the topic under the spotlight and has sparked discussions among not only in the academia, but also in the industry and the public.

The outbreak of the COVID-19 pandemic has changed the world in many perspectives. It is widely accepted that vaccination will be a key strategy to bring the world back to normalcy. The major question or the concern is how long the protection induced by vaccines for SARS-CoV-2 can last. Here, we aim to approach major questions regarding the longevity of vaccine-induced protection by reviewing the basic concepts and major progress in the field of vaccine immunology.

1.1 | How does the immune system respond to vaccines?

Most current vaccinations confer protection via eliciting the production of pathogen-specific antibodies, which target specific epitopes in pathogens or their toxic components.[10] Antibodies are exclusively produced by a specific subset of B lymphocytes called plasma cell (PC). The generation of PC is a complex process requiring the involvement of multiple immune types in both the innate and adaptive immune systems. The antibody response upon vaccination is initiated when B cells are activated by vaccine antigens, which majorly occur in secondary lymphoid organs (SLOs) including spleens, lymph nodes (LN), and Peyer’s patches. In brief, vaccine antigens reach the draining LN of the injection site where they are captured by specialized macrophages in the subcapsular region and then transported to B-cell zone (follicles). B cells with specific B-cell receptor (BCR) that recognize the antigens are activated. Activated B cells migrate toward the border region between B-cell follicles and T-cell zone, where they present processed antigen and engage with CD4+ T cells that also recognize the same antigen and receive help signals to support their proliferation and differentiation.[11] Activated B cells can give rise to extrafollicular response which leads to the production of short-lived PCs or germinal centre (GC) response that supports the production of high-affinity and long-lived PCs and memory B cells (Figure 1). These will be discussed in detail.

In parallel to the activation of B cells, CD4+ T cells are activated by T-cell receptor signaling through antigen peptides presented by the major histocompatibility complex (MHC) class II of antigen-presenting cells (APCs) such as dendritic cells (DCs) and costimulatory signaling from APCs[12] (Figure 1). Activated CD4+ T cells can differentiate into effector subsets with distinct functional profiles.[13] CD4+ T-cell effector subsets were initially categorized into type 1 helper T cells (Th1) and type 2 helper (Th2) based on the expression of signature cytokines (IFN-γ for Th1 and IL-4 for Th2).[14] In the past decades, several new effector CD4+ T-cell subsets were identified, with follicular helper T (Tfh) cell as the key subset to support B cells in antibody responses. They localize proximal to B-cell follicles and express high amounts of CD40 ligand (CD40L) and interleukin-21 (IL-21) to stimulate B cells. The differentiation and function of Tfh cells have been reviewed elsewhere.[15–17] APCs especially DCs play a pivotal role in providing instructive cues including cytokines and costimulatory signals for the differentiation of effector CD4+ T-cell subsets. However, the mechanism guiding the differentiation determination of Tfh cells by APCs is only partially understood. The types of antigens and adjuvants in vaccines were shown to modulate APC activation and function, thus, subsequently shaping Tfh differentiation.[18–21]

During the early stage of vaccination responses, extrafollicular PCs are generated by T-cell—B-cell interactions at the border of T-cell zone and B-cell follicles.
FIGURE 1 The vaccine-induced immune responses. Upon vaccination, the vaccine antigens reach the SLOs which are compartmentalized into specific regions including marginal zone (MZ), B-cell follicle, and T-cell zone. (1) B cells in MZ can give rise to short-lived PCs responding to bacteria LPS antigens in the absence of T helper cell (Th). (2) The naïve follicular B cells are activated by the antigens processed by macrophages, and migrate toward the T-B border. (3) The naïve CD4+ T cells are primed by the antigens presented by APCs, such as DC, in combination with costimulatory signals, which drive the functional differentiation of Th cells. (4) The Th cells provide helper signals to B cells in the T-B border, generating short-lived extracellular PCs or (5) by committing T-FH differentiation, support the (6) initiation and maintenance of GC responses. (7) By receiving the selection signals elicited by BCR and T-FH cells, the GC B cells undergo robust proliferation, SHM, or commit terminal differentiation into LLPCs secreting high-affinity antibodies or (8) memory B cells. Besides, naïve CD8+ T cells can be activated by the antigens cross-presented by DC, which drives the differentiation into (9) short-lived effector cells or (10) persistent memory cells.

Partially differentiated T-FH cells, with the help of T-H1 and T-H2 cells, support extracellular PC production [22,23] (Figure 1). Type 1 cytokine IFN-γ produced by T-FH and T-H1 cells induce the isotype class switching to IgG2 in mice and IgG1/IgG3 in human; while type 2 cytokine IL-4 produced by T-FH and T-H2 cells induce drives IgG1 and IgE in both mice and human [22,24]. Notably, certain vaccines, such as live attenuated vaccines, could induce extracellular antibodies by antigens, such as bacterial lipopolysaccharide (LPS), without the help of T cells (Figure 1). Such thymus-independent responses produce most IgM with limited isotype switching [25]. Without affinity maturation, most extracellular antibody responses produce antibodies with low to modest affinity to antigens. And importantly, they decay rapidly [22]. Therefore, successful vaccination is primarily dependent on the formation of GCs.

Long-lived PCs (LLPCs) secreting high-affinity antibodies and memory B cells are exclusively generated from
specialized lymphoid structures within B-cell follicles termed GCs.\textsuperscript{[11,26–28]} The presence of GC-TFH cells is necessary for the initiation and maintenance of GCs by providing critical costimulatory signals via CD40L and cytokines such as IL-21.\textsuperscript{[29–32]} GC B cells undergo extensive somatic hypermutation (SHM), whereby mutations are introduced into the variable region of the Ig genes.\textsuperscript{[33]} The accumulation of mutations associated with diversified antigen-binding affinity enables those GC B cells to differentially compete for limited antigens retained by follicular dendritic cells (FDC).\textsuperscript{[34,35]} By capturing antigens and presenting processed antigen to T\textsubscript{FH} cells, GC B cells compete for help from T\textsubscript{FH} cells which is required for the survival and proliferation of GC B cells. Multiple rounds of the selection process in GCs confer GC B cells that have developed a high affinity to vaccine antigens to outcompete the rest, a process named affinity maturation.\textsuperscript{[11]} Eventually, a small fraction of GC B cells exit after succeeding in the selection and committing terminal differentiation into LLPCs or memory B cells\textsuperscript{[36,37]} (Figure 1). The fate decision of GC B cells is critical for the success of the formation of high-affinity and long-lived humoral immunity induced by vaccination. The underlying mechanisms are under active investigation, with recent progress suggesting that the strength of signaling lying mechanisms are under active investigation, with humoral immunity induced by vaccination. The under-

success of the formation of high-affinity and long-lived effector cells are short lived and enter programmed cell death at the end of primary immuneresponses. In contrast, memory CD8\textsuperscript{+} T cells persist over a longer period, and they can rapidly proliferate into a massive wave of effector cells upon the re-exposure to the same pathogen.\textsuperscript{[41,42]} The memory function of CD8\textsuperscript{+} T cells have been suggested to be a major protection mechanism for the elderly with inadequate antibody responses post influenza vaccination.\textsuperscript{[43]} A new subset of CD8\textsuperscript{+} T cells was identified to persist in nonlymphoid tissues for an extended period and control reinfection. Termed as tissue-resident memory T cells (T\textsubscript{RM}), they are of great interest for the development of vaccines against infections entering through respiratory and digestion tracts where conventional antibody-based vaccinations are unable to induce sufficient capacity to neutralize pathogens during initial infections.\textsuperscript{[44]} Taken together, the understanding of fundamental vaccine immunology is the cornerstone to conceive approaches to design vaccines that effectively orchestrate both innate and adaptive immunity against pathogens.

### 1.2 How to measure vaccine-induced protection

As described above, vaccination stimulates a complex immune response which raises the question how to measure vaccine-induced immunity. Verification of vaccine’s safety and effectiveness, that is, induced immunity against infection, is a time-consuming process in the development of vaccine, which requires extensive research in preclinical animal models and clinical trials. Notably, it is not always feasible to measure immunity as the end-point of clinical trials, due to the emergency of infectious diseases such as COVID-19 or infections with prolonged latency period.\textsuperscript{[45,46]} Therefore, clinical trials for vaccines often adopt immunological correlates of protection (CoP), which are critical parameters of laboratory tests being statistically associated with the protection from the occurrence of clinical diseases to assess vaccine efficacy. Historical nomenclature systems in defining CoP were distinct and ambiguous.\textsuperscript{[47,48]} A more recent unified terminology was proposed to classify CoP into mechanistic correlates (mCoP) and nonmechanistic correlates (nCoP), based on whether identified immune parameters (correlates) are responsible for protection.\textsuperscript{[49]}

Among a wide range of vaccine-induced immunological changes in both humoral and cellular immunity, it is widely accepted that long-term antibody responses confer the major protection by most vaccines. Mechanistically, vaccine-induced antibodies in the circulation and mucosa can effectively neutralize extracellular pathogens and thus, prevent dissemination once entering inbody.\textsuperscript{[10]} Therefore, the serum or plasma titer of neutralizing antibody is the major mCoP for most vaccines.\textsuperscript{[45]} The titer can be measured by enzyme-linked immunosorbent assay (ELISA), hemagglutination, or neutralization assays, whereby a threshold of protective titer was characterized for each vaccine. Antibodies could execute protection beyond neutralization, so neutralization antibodies titer does not always indicate vaccine efficacy. For example, in the experimental trial of HIV vaccine candidate, RV144, the protection was shown to positively associate with the levels of specific vaccine antigen-specific isotypes including IgA and IgG\textsubscript{3} and the capacity of antibody-dependent cellular cytotoxicity (ADCC).\textsuperscript{[10]} In certain vaccines for pneumococcal, meningococcal, and influenza infections, the measurements of immune functions for opsonophagocytosis and bactericidal activity were found to be more predictive of the efficacy of protective immunity than neutralization titer alone.\textsuperscript{[50]}
### Table 1  The protection duration and correlates of protection of major vaccines

| Vaccines          | Vaccine type                | Estimated protection duration | Major CoP                              | References |
|-------------------|----------------------------|-------------------------------|----------------------------------------|------------|
| Diphtheria        | Toxoid subunit             | Over 20 years                 | Antibody titer measured by neutralizing assays | [66]       |
| Hepatitis B       | Subunit                    | Over 10 years                 | Antibody titer measured by ELISA       | [95]       |
| HPV               | VLP                        | Over 10 years                 | Antibody titer measured by ELISA       | [70]       |
| Influenza         | Killed virus, subunit      | Decline within 1 year         | Antibody titer measured by hemagglutination Inhibition assay | [7, 67]   |
| Measles           | Live-attenuated            | Over 10 years                 | Antibody titer measured by ELISA       | [66]       |
| Meningococcus     | Subunit                    | Decline within 1 year in infants | Antibody titer measured by bactericidal assays | [96]       |
| Mumps             | Live-attenuated            | Decline within 10 years       | Antibody titer measured by neutralizing assays | [66]       |
| Pertussis acellular | Subunit                  | Decline within 2 years        | Antibody titer measured by ELISA       | [97]       |
| Poliomyelitis (Sabin) | Live-attenuated        | Over 10 years                 | Antibody titer measured by neutralizing assays | [98]       |
| Rubella           | Live-attenuated            | Over 20 years                 | Antibody titer measured by ELISA       | [66]       |
| Smallpox          | Live-attenuated            | Over 10 years                 | Antibody titer measured by neutralizing assays | [66]       |
| Tetanus           | Toxoid subunit             | Over 20 years                 | Antibody titer measured by neutralizing assays | [66]       |
| Tuberculosis (BCG) | Live-attenuated         | Over 10 years                 | CD4⁺ T-cell responses                  | [98]       |
| Yellow fever      | Live-attenuated            | Over 10 years                 | Antibody titer measured by neutralizing assays | [99]       |

such as Chlamydia and Mycobacteria, where the level of neutralization antibody poorly correlated with the protection, evidence suggested cellular immunity-mediated T cells are required.\cite{51} Data suggest that the production of interferon-γ by (CD4⁺ or CD8⁺) T cells was identified as the major mCoP of the Bacillus Calmette–Guérin (BCG) vaccine for the protection of tuberculosis infection.\cite{52} Intriguingly, BCG vaccine has been shown to reprogram innate immunity so that “trained immunity” can mediate nonspecific protection to heterologous pathogens such as respiratory viral infections.\cite{53, 54} Indeed, BCG vaccine has been conceived and trialed to protect patients from severe disease of SARS-CoV2 infection.\cite{55} In conclusion, the identification of specific CoP for each vaccine is not only necessary to assess vaccine efficacy for development and approval, but also very useful to investigate the longevity of vaccine-induced protection (Table 1).

### 1.3 The duration of vaccine protection

While most of us are eager in expecting the success of vaccine for SARS-CoV2, some concerns are building up due to reported cases of reinfection, which raised the question for the longevity of protection upon vaccination.\cite{56} While several COVID-19 vaccines have completed their Phase-III clinical trials and demonstrated encouraging protective efficacies ranging from 67 to 95%,\cite{57} and some of which have been applied for global implementation, it remains unclear whether these vaccines can offer long-lasting protection. Given the urgent nature of developing SARS-CoV2 vaccines, current data were mostly obtained from an observation period of around 120 days post the first dose of vaccine administration.\cite{58-61} Longitudinal studies with extended observation period, therefore, are required to identify the longevity of vaccine-induced protection. Moreover, SARS-CoV2 virus is susceptible to rapid mutations, and recent reports have identified severely impaired vaccine protection against the B.1.351 variant in NVX-CoV2373 (efficacy = 51%)\cite{62} and even loss of protection for ChAdOx1 nCoV-19 (efficacy = 10.4%).\cite{63} The concerning data suggest the need of developing novel vaccines targeting a broader range of antigenic epitopes.

To many, it might be surprising to know that, for most vaccines, there is no accurate answer for the longevity
of protection after a vaccination. First of all, it is difficult to design and execute a longitudinal study to track vaccine populations over a decade or longer to collect data and address this question. Second, the broad implementation of vaccination scheme in many countries has established herd immunity for certain infectious disease so that the protection remains despite individuals’ immunity declines.[64] Furthermore, declined immunity-induced by vaccination might still confer a partial protection. As a result, a subsequent infection might be mild or even asymptomatic.[65]

Although most vaccines were approved and implemented before a clear understanding of the actual durability of protection, studies collected indirect evidence and provided significant insights. In a seminal longitudinal research to track 45 subjects over 26 years, antibody titers for common virus and vaccine antigens were analysed.[66] Results showed antibody titers induced by vaccine antigens appeared weaker than those resulted from natural infections. In particular, the antibody responses against tetanus and diphtheria antigens were found to decline with half-lives of 11 and 19 years, respectively. The authors admitted a limitation of the small sample sizes, such as only two to five subjects, for the vaccinations of measles, mumps, and rubella so that statistical significance was poor. Future study of this kind but with larger cohorts will help to provide more meaningful comparison between vaccination and natural infection.[66]

Compared to decade-long protection induced by tetanus and diphtheria vaccines, many studies have provided evidence indicating a rapid waning of protection within one season after vaccination for seasonal influenza virus.[7,67] Although the speed of declination of influenza vaccination-induced immunity varies in multiple reports as distinct vaccines and methodologies were involved.[68] Timing of vaccination should aim to achieve the highest level of protection during peak influenza season. Therefore, vaccination is recommended only 3 to 4 months before peak influenza season. Growing evidence also revealed that the protection by other important vaccines also waned faster than what had been previously suggested by official immunization recommendation[68] (Table 1). The waning of vaccine-induced immunity over time could result in epidemics of infectious diseases. Since 2006, resurgence of mumps infections has been recorded in USA. Majority of these cases were school-aged children who had already received two doses of mumps vaccination.[91] The insufficient protection aroused the public concern. Correspondingly, in 2018, The Advisory Committee on Immunization Practices (ACIP) started to recommend a third dose of mumps booster vaccination for people at increased risk of exposure to the infection.

In contrast, prolonged immunity was reported for other vaccines including those against smallpox, rubella, and human papillomavirus (HPV).[66,69,70] (Table 1). The reasons for varied durability of protection induced by different types of vaccines remain not completely understood. We will discuss some explanations in the next part. Understanding mechanisms underlying the persistence of vaccination-induced protection can guide the design of better vaccines.

1.4 What determines the longevity of vaccine protection and how to improve it

Durable protection induced by vaccination essentially relies on memory humoral immunity, which is composed of two major components: pathogen-specific antibody produced by LLPCs and anamnestic responses upon antigen re-exposure whereby memory B cells are rapidly reactivated and differentiate into a significant number of PCs secreting high-affinity antibody.[71] Therefore, a stronger generation and a better maintenance of LLPCs and memory B cells can prolong vaccine protection.

Compared to memory B cells, the survival of LLPCs is better understood. After leaving GCs, LLPCs migrate into bone marrow where they seek special niches with the support of stromal cells for long-term survival.[72] Although the antibody level after a given vaccination reaches the peak at around 1 month and gradually declines, it stabilizes as a plateau much higher than the level prior to vaccination which is largely contributed by the continuous production from LLPCs in bone marrow. LLPCs are responsible for maintaining antibody levels in animal models of vaccination and were recently shown to directly correlate with vaccine-induced protection in humans. Davis et al. demonstrated that although the vaccine for influenza virus can induce the generation of PCs in bone marrow, they rapidly decline to baseline level within 1 year.[73] The relatively short life-span of PCs in bone marrow after influenza vaccine can explain unsustained antibody titer and rapid decay of protective immunity after seasonal influenza vaccination.[7] Little information is available for the longevity of PCs induced by other vaccines, authors in this study suggested that the phenomenon of rapid LLPC waning in bone marrow might not be unique for influenza vaccination but might also be found in other vaccines. On the other hand, the persistence of memory B cells induced by vaccine remained even more unclear and is subject to further investigation.

Given few if any approach has been developed to promote the survival and maintenance of LLPCs and memory B cells, strategies to enhance vaccine efficacy and prolong the subsequent protection have been focusing
FIGURE 2 The factors associated with prolonged vaccine-induced antibody responses. The persistence of vaccine-induced antibody protection essentially relies on the maintenance of serum neutralizing antibodies titer above the protection thresholds. Therefore, the longevity of antibody protection can potentially be improved through: (1) enhancing the potency of primary antibody responses, which generate an increased number of LLPC and more sustained antibody titer. Using antigens with strong immunogenicity such as live-attenuated antigen and VLPs-based antigens and including adjuvants in the formulation contribute to enhancing the primary responses. (2) Antibodies with improved affinity/avidity, neutralizing efficacy or functionalities, such as ADCC, can lower the protection threshold of the serum titer, and therefore, provide extended protection even under declined titers. The neutralizing efficacy differed in antibodies targeting distinct epitopes, therefore, rationally designing and engineering antigens to specifically inducing high-quality antibodies represent a promising strategy for improving the longevity and efficacy of vaccine-induced immunity. (3) The anamnestic responses of memory B cells upon re-exposure to the antigen by booster shots can rapidly produce a large number of PC and secreting antibodies with higher affinity, which can enhance the persistence of antibody protection by increasing serum titer and reducing the protection threshold simultaneously on strengthening the magnitude of antibody response induced by vaccination (Figure 2). To generate higher titer of antibody and more LLPCs as well as memory B cells, optimal activation of B and T cells are required, which will lead to strong GC and TFH responses.\textsuperscript{[74–77]} The immunogenicity of vaccine is a major factor to determine B- and T-cell activation and largely influenced by which platform vaccines are delivered. There are six major vaccine platforms, which can be divided into live (live-attenuated vaccines) and non-live (inactivated vaccines, subunit vaccines, recombinant viral vector vaccines, virus-like particle [VLP] vaccines, and nucleic acid-based vaccines) categories. The features of safety and efficacy for each vaccine platform have been extensively reviewed elsewhere.\textsuperscript{[78]} Notably, although vaccines using recombinant viral vector and nucleic acid-based platforms have shown great promise for SARS-CoV-2, particularly, the ongoing global implementation of adenoviral based vaccines (ChAdOx1) and mRNA-based vaccines (BNT162b2) to SARS-COV2 could potentially introduce paradigm-shifting advances in the vaccine development, these two types of vaccines have not been used in previously
approved vaccines with scarce knowledge for their potency and durability.[78] Besides, the reported cases of thrombocytopenia after the adenoviral vector-based ChAdOx1 vaccination raised significant safety concerns.[79] For vaccine platforms commonly in use, it is well documented that live-attenuated vaccines with weakened pathogens (e.g., smallpox and poliomyelitis), even by a single immunization, can induce strong and long-lasting antibody responses. Live-attenuated vaccines can elicit intensified innate immune responses through pathogens' pattern molecules, such as Toll-like receptors (TLRs), thus, subsequently enhancing B- and T-cell activation.[3]

In contrast, non-live vaccines represented by inactivated pathogens (e.g., influenza and rabies) and subunit vaccines (e.g., hepatitis B virus) usually show poorer immunogenicity. To overcome such limitation, non-live vaccines are often formulated by adding adjuvants and administered using prime-boost vaccination regimens. Adjuvants stimulate the innate immunity to optimize the priming of B and T cells by vaccine antigens.[3] The few types of adjuvant licensed for human use are shown to induce distinct potency and persistence of immunological responses, presumably by eliciting distinct signaling in the innate immune cells. For example, the AS04 adjuvant developed by GlaxoSmithKline (GSK) contains the mixture of alum and monophosphoryl lipid A, which stimulates TLR4 signaling while alum alone activates NLRP3 inflammasome independent of TLRs.[80,81] In a comparison between two HPV vaccines: Cervarix (GSK, using AS04 as adjuvant) and Gardasil (Merck, using alum as adjuvant), AS04 is shown to induce more robust and persistent protective immunity.[82] The immunogenicity of vaccines can also be enhanced by increasing the valency of vaccine antigen. One example is HPV vaccines, which induce antibody responses that can last for decades.[70] As the type of VLP vaccine, HPV vaccines are supramolecular nanoparticles containing highly repetitive HPV viral capsid protein L1 or L2 on the surface,[83,84] which potently stimulates B-cell activation by inducing efficient BCR crosslinking.[85,86] Recently, Kato et al. demonstrated that the high antigen valency of VLPs can significantly promote the early B-cell activation and the persistence of GC responses, which lead to enhanced LLPC differentiation.[75] Thus, VLP-based vaccine represents a superior strategy to vaccine development and has been adopted for HBV and more recently SARS-COV-2.[78]

Compared to live-attenuated or VLP-based vaccines, antibodies induced by conventional inactivated vaccines and subunit vaccines likely waned faster. The immediate question is what level of residual antibody is sufficient to prevent the infection and spread of real pathogens, that is, the protection threshold of pathogen-specific antibody level. For example, the protection titers of neutralizing antibodies against tetanus and diphtheria were reported lower than 0.01 IU/mL. Therefore, even though antibodies induced by toxoid subunit-based vaccines decay significantly with a half-life of 10–20 years, long-term protection was maintained for most vaccine recipients.[66] Notably, a suboptimal titer of pathogen-specific antibodies can, however, cause antibody-mediated enhancement of diseases. A case in point is the Dengue virus vaccine, where subneutralizing titer of antibodies to one serotype of virus can enhance the infection of other serotypes via the Fc-γ receptor-mediated phagocytosis in cells such as macrophages.[87] Therefore, the protection threshold for antibodies induced by vaccination can vary drastically and is also a crucial factor to determine the longevity of protection (Figure 2). For neutralizing antibodies, the protection threshold at least partially depends on antibody affinity or avidity and the target epitope in the antigens.[88] While our understanding on how the quality of antibody responses are regulated are far from clear, the emerging technology based on the knowledge of structural features of vaccine antigens and epitopes recognized by neutralizing antibodies has achieved promising progress. For example, the engineered respiratory syncytial virus F protein, which is stabilized in a structure exposing the neutralizing-sensitive epitopes, is shown to induce highly potent neutralizing antibodies.[89] Such rationale-based vaccine design has been made to benefit the induction of high-quality antibodies so that a lower protection threshold can be achieved.

If resident antibodies induced by vaccination are insufficient to completely prevent the replication of pathogens upon infection, memory B cells and T cells generated by vaccination will kick in to mount memory immunity (Figure 2). The persistence of memory B cells has also been extensively studied for the long-term protection of vaccination. It has been reported that recipients of HBV vaccine are largely protected from infection by memory response even after HBV-specific antibodies from the primary response have significantly dropped.[90] Since memory B cells are generated from GC responses upon vaccination and have undergone affinity maturation, they rapidly differentiate into a significant number of PCs upon infection to produce high-affinity antibodies to target pathogens.[71] Therefore, the optimal generation of memory B cells using suitable vaccine platforms including adjuvants for specific pathogen should be considered.[3] Many vaccinations apply the “prime-boost” immunization regimen for the purpose of multiple rounds of amplification of antibody response and enhanced affinity maturation. It should be noted that, during a boosting immunization, the existence of high level of neutralizing antibodies can reduce the accessibility of memory B cells to vaccine antigens. Therefore, longer intervals between two immunizations
are commonly applied, such as the common “prime-boost” regimen of “0-1-6” with two boost immunizations 1 and 6 months after the primary immunization.

T-cell memory induced by vaccination can also contribute to the protection of infection. Memory TFH cells have been characterized using human blood and were found to be associated with the efficacy of influenza vaccination. The mechanism regulating the differential generation of mature TFH cells and memory TFH cells during vaccination is an area that needs further investigation. Recent advances in SARS-CoV-2 infection identified viral-specific memory T cells in a large fraction of convalescent patients, indicating the contribution of T-cell memory in the optimal immune protection upon SARS-CoV-2 infection. However, whether T-cell memory responses are involved in the SARS-CoV-2 vaccine-induced protection remains to be further elucidated. Encouraging result has shown efficient viral clearance by CD8+ T cells specifically activated by advanced vaccine antigen target delivery system.

2 | CONCLUDING REMARKS

Although vaccination has contributed to eliminate some major infectious diseases and help to control others, significant questions remained due to the incomplete understanding of vaccine immunology. Even for available vaccines, immune responses vary among individuals and are often insufficient to populations vulnerable for infectious diseases such as infants, elderly, and people with pre-existing comorbidities. The longevity of protection is an important question to assess the efficacy of different vaccines and the effectiveness in distinct populations. The identification of reliable CoPs and the design of strategies to achieve long-term protection essentially rely on the progress in the understanding of vaccine immunology.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Dr Zhian Chen is a Postdoctoral Research Fellow in Professor Di Yu’s group at University of Queensland Diamantina Institute in Brisbane, Australia. He received his PhD degree from the Biomedicine Discovery Institute (BDI), Monash University in 2017 and started his postdoctoral research under the supervision of Professor Di Yu since 2018 in John Curtin School of Medical Research (JCSMR), Australian National University and moved to UQ Diamantina Institute with the lab in 2020. His current research focuses on revealing novel mechanisms modulating T cell dependent humoral immunity and developing new strategies for immunotherapies.

Dr Di Yu is a Professor of Immunology at the University of Queensland Diamantina Institute in Brisbane, Australia. He received his PhD from Australian National University in 2007 and postdoctoral training at the Garvan Institute of Medical Research from 2008–2010. Before joining the University of Queensland, he was a faculty member at Monash University from 2011–2016 and Australian National University ANU from 2017–2019. In the Laboratory for T-cell Immune Mechanism, Monitoring and Modulation (TIM3), Professor Yu and his team investigate the mechanisms that regulate the functions of T cell subsets in human health and disease and aim to design new strategies to monitor personal immune status and modulate immune pathways to treat autoimmune diseases, cancer and infection. He has published in high impact journals including Nature, Nature Immunology, Nature Medicine and Immunity and is recognised as Global Highly Cited Researcher (2019, 2020) by Clarivate and Web of Sciences.

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